Fetal Programming and Wilms Tumor

Julia E Heck [1,2], Di He [1], Carla Janzen [3], Noah Federman [4], Jorn Olsen [5], Beate Ritz [1], Johnni Hansen [6]

1. Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, USA
2. Jonsson Comprehensive Cancer Center, University of California, Los Angeles, USA
3. Department of Obstetrics and Gynecology, Geffen School of Medicine, University of California, Los Angeles, USA
4. Department of Pediatrics, Geffen School of Medicine, University of California, Los Angeles, USA
5. Department of Clinical Epidemiology, Aarhus University, Denmark
6. Danish Cancer Society Research Center, Copenhagen, Denmark

Correspondence:
Julia E Heck
Department of Epidemiology
650 Charles E. Young Drive, Box 951772
Los Angeles, CA 90095-1772
(Tel) +1 (310) 825-4254
Email: jeheck@ucla.edu

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Abbreviation	**Full term**
OR	Odds Ratio
CI	Confidence Interval
PLNR	Perilobar nephrogenic rests
ILNR	Intralobar nephrogenic rests
LGA	Large for gestational age
SGA	Small for gestational age
ICCC	International Classification of Childhood Cancer
ICD-O	International Classification of Diseases for Oncology
ICD	International Classification of Disease
BMI	Body mass index
Grb10	Growth Factor Receptor Bound Protein 10
IGF2	Insulin growth factor
IGF-1	Insulin-like growth factor-1
TNF-α	Tumor necrosis factor-α

Abstract

Background: The 'fetal programming' hypothesis has been evaluated in many adult diseases including cancer, but not for Wilms tumor. Wilms tumor has been related to high birthweight but little is known about other growth metrics such as a baby's birth length, ponderal index, or placenta size, which can shed additional light on growth patterns.

Methods: Cases of Wilms tumor (N=217) were taken from the Danish Cancer Registry, and controls (N=4,340) were randomly selected from the Population Register and matched to cases by sex and age. Linkage to the Medical Births Registry provided information on gestational factors and fetal growth measurements, while linkage to the Patient Register provided information on maternal and child health conditions.

Results: Despite having typically normal to higher birthweights, Wilms tumor cases had smaller placentas (≤540g; Odds Ratio (OR) = 4.24; 95% Confidence Interval (CI) 1.84, 9.78) and a lower placenta to birthweight ratio (OR =1.81; 95% CI 1.17, 2.82, per 1 SD decrease). Small placentas were more common among Wilms cases without congenital anomalies (OR = 6.43; 95% CI 1.95, 21.21). Wilms tumor cases had a higher prevalence of high birth weight (>4000 g; OR = 1.57; 95% CI 1.11, 2.22), birth length 55cm or longer (OR = 1.74; 95% CI 1.09, 2.78), and being large for gestational age (OR = 1.79; 95% CI 1.08, 2.96).

Conclusions: Our study corroborates earlier studies showing associations with high birthweight, and suggests associations between Wilms tumor and decreased placental size and low placenta-to-birthweight ratio.

Introduction

Increasing evidence points to in utero and early life exposures as important determinants of some aspects of health through the life course. This 'fetal programming' or 'fetal origins' hypothesis links antenatal factors, including xenobiotic exposures, stress, or diet to altered fetal development and later life health status via programming of biological and physiological changes. Applications exploring this hypothesis have suggested that markers of early growth including placental morphology and child's body size at birth are predictive of diseases later in life.[1-3]

Wilms tumor (or nephroblastoma) is a malignant tumor arising from pluripotent embryonic kidney precursor cells or the metanephric mesenchyme, which comprises 95% of renal cancers diagnosed among children younger than 15 years of age.[4] Most Wilms tumor is sporadic (98-99%),[5] and in the United States incidence is highest in African-American (7.1 per million), followed by White (6.1 per million) children, with a lower incidence in Asian/Pacific Islander and Native American children (3.0 and 3.5 per million, respectively).[6] Wilms tumor sometimes arises in kidneys with perilobar nephrogenic rests (PLNR) or intralobar nephrogenic rests (ILNR), representing differing stages of renal development, with INLR's representing an earlier stage of developmental disturbance.[7] Wilms cases with INLR's are diagnosed at earlier ages (most often <3 years) compared to cases with PLNR's and are more common in males than in females.[8,9]

Congenital anomalies and syndromes are reported in some children who develop Wilms tumor but make up a minority of all cases. The National Wilms Tumor Study Group reported that, among the most commonly reported co-occurring conditions, Beckwith-Wiedemann syndrome is present in 1% of Wilms tumor cases, aniridia in <1%, and cryptorchidism and hemihypertrophy each in 2.5% of cases.[10,11] Suspected risk factors for Wilms tumor include maternal hypertension, exposure to pesticides, and parental exposure to hydrocarbon solvents;[12,13] but only a few purported risk factors have been studied in depth.

In part due to its relation with overgrowth syndromes, Wilms tumor is frequently related to high birthweight (>4000g). High birthweight occurs among cases with and without congenital anomalies,[14] although Wilms tumors that occur in a kidney with ILNRs are associated with lower birthweight.[8] Apart from birthweight, there have been few reports on the relation between fetal growth and Wilms tumor. Increases in risk with large for gestational age (LGA) were reported, while results for small for gestational age (SGA) were mixed.[15-18] Surprisingly for a cancer related to overgrowth, Wilms tumor was weakly related to low ponderal index in one study, while there was no association reported with either larger head circumference (≥39 cm) or longer birth length (≥54 cm).[16]

Early growth deviations may be important for later cancer risk but few published studies have examined a variety of growth metrics. An earlier Scandinavian study utilized some of the same cases as included in the present study, combining Danish data with other Registries in Norway and Sweden,[16] however the use of multiple Registries limited the number of variables available for pooling. The present study also adds 14 additional years of cancer data. The purpose of this study is to examine detailed metrics of fetal growth in relation to Wilms tumor risk.

Methods

Data from this study was derived from record-linkage of several national databases,[19] with linkage occurring via the unique personal identification number assigned by the national

Central Population Registry (established 1968) and given to each person residing in Denmark; this register links parents to their children. We ascertained childhood cancer cases (age<20 years) listed in the Danish Cancer Registry.[20] Wilms tumor cases (N=217) were identified with International Classification of Childhood Cancer (ICCC-1 and ICCC-3) code 61 and International Classification of Diseases for Oncology (ICD-O-1 and ICD-O-3) code 8960/3. Controls (N=4340) free of cancer at the date of their corresponding case's diagnosis, were matched (20:1 ratio) to cases on sex and year of birth and selected at random from the Central Population Register, as previously described.[19] In order to have as complete information as possible from available Registers on gestational and parental information, study inclusion criteria were that all cases and controls were born in Denmark.

Family socioeconomic status information was taken from the Central Population Register and was based upon fathers' and mothers' job titles from income tax forms, with the family's socioeconomic status classified based on the higher of the two parent's job titles. Due to changing requirements on tax forms, job title was reported less frequently in the latter part of the study period. Wilms tumor incidence is highest in African and European-origin populations,[6] however we do not have information on the ethnic background of families, hence we examined risk based on a proxy of ethnic heritage: whether parents were born in Denmark, vs. other European countries or North America, vs. other nations; low immigration prior to the 1980's suggests that most children in our study of African or Asian heritage would have had parents born outside of Denmark.[21] Small numbers precluded examination of risk among children with African-origin parents separately, as only one case had an African-born parent.

The present analysis was limited to children with data available from the Medical Births Registry (computerized 1973+) which provided information on fetal growth and other gestational factors.[22] This Register's data were collected from midwives until 1996, after which time most variables were automatically taken from the Hospital Register, with some exceptions including smoking, which continued to be reported by midwives. Not all variables were collected in each year. We ascertained gestational age from this register, using multiple imputation to estimate this variable when it was missing, using a model which included birthweight, sex, maternal smoking, placenta weight, presence of anomalies, birth length, place of birth, complicated or normal delivery, and interventions during pregnancy. In a validation analysis of imputed gestational ages, we compared imputed gestational ages and actual gestational ages by applying our imputation model to the data for children where gestational age was non-missing. We observed that the predicted gestational age (days) averaged 277.0 days (s.d., 7.4) while the actual gestational age in days was 277.2 (s.d. 13.0); r=0.62. Very preterm children (<30 weeks gestation) were less likely to have gestation lengths predicted with accuracy. Imputation was only done for gestational age, with no other variables imputed.

After a literature review of the fetal programming hypothesis and chronic disease outcomes, we decided *a priori* to include all available fetal and placenta growth variables in analyses. We additionally decided *a priori* to report on maternal height, weight, and body mass index (BMI) since these maternal factors impact fetal growth, and only a limited literature has examined maternal body size in relation to cancers in children. We defined ponderal index as fetal weight (kg) / fetal length $(cm)^3$. Placenta to birthweight ratio was derived by dividing the placental weight by birthweight, while head to abdominal circumference ratio was derived by dividing head circumference by abdominal circumference. The variable "mother's risky behavior before birth" was reported by midwives and was intended to indicate risk factors present for the woman which suggested that the woman needed to give birth at a specialized obstetric department. Size at gestation was considered as small if birth weight was less than the 10th percentile and as large if greater than 90th percentile of the birthweight standards for a given gestational age. The 10th and the 90th percentile values were obtained for each gestational week (20-45 weeks) by child's sex and birth year based on the total singleton live births in Denmark between 1981 and 2004, using a method described previously.[23]

Information on mother's and child's hospitalized diseases was taken from the National Patient Register (1977+), which utilized International Classification of Disease version 8 (ICD-8) codes until 1993, and an extended version of ICD-10 thereafter. Procedure codes utilized a Nordic coding system from 1977-1995, and an extended version of ICD-10 thereafter.[24] We searched this Register for diagnoses of congenital malformations in the child. Congenital malformations were identified with ICD-8 codes (740xx-759xx) and ICD-10 codes (Q00-Q99) as listed in the Patient Register or the Medical Births Registry, or when midwives identified the children at birth as having any congenital anomaly. Because preliminary data suggested some evidence of altered placenta size among cases, we additionally examined the prevalence of maternal conditions that are related to altered placenta size.[25,26] ICD-8 and ICD-10 codes used to identify these conditions are listed in Supplementary Tables S1 and S2. To ascertain mothers with these conditions, we only included families where at least one full trimester of the index pregnancy occurred after the establishment of the National Patient Register in 1977.

We categorized variables into quantiles based on the distribution in controls, and sometimes collapsed stratum that had small numbers of cases. Odds ratios and 95% confidence intervals were derived via conditional logistic regression. We estimated adjusted effects only when there were more than 5 cases in a category. Consideration of factors for adjustment was based on literature review as well as examination of the data. Because the placenta grows in tandem with the fetus across pregnancy, in adjusted analyses examining placental weight, we adjusted for birthweight (continuous); apart from analyses of placental weight, we did not adjust for birthweight as it may be an intermediate in the cancer pathway.[27] All other analyses were adjusted for gestational age (continuous). We considered additional adjustment for Wilms tumor risk factors [12] and factors related to infant and placenta size,[26,28] including maternal and paternal age, area of residence, maternal smoking, maternal risky behavior before birth, maternal body mass index (BMI), parity, birth order, and parental place of birth, but the inclusion of these variables did not change effect estimates by >10% and were left out of final models.

In sensitivity analyses, we examined the associations with fetal growth metrics among children without congenital anomalies (Supplementary Table S3). We additionally conducted stratified results by age at diagnosis (± 3 years) as shown in Supplementary Tables S4 and S5; children diagnosed at a younger age are more likely to have multifocal tumors, bilateral disease, genitourinary anomalies, aniridia, and ILNR, while children diagnosed at an older age have a higher prevalence of hemihypertrophy and PLNR.[8,29] Other studies have shown variation in Wilms tumor and other pediatric cancer risk factors by age at diagnosis.[16,18,30,31] We additionally conducted sensitivity analyses to examine results when multiple imputation was not used for gestational age, but findings did not change (Supplemental Table S6).

Results

Demographic and maternal characteristics are shown in Table 1. There was little evidence that parental age or socioeconomic status was related to Wilms tumor. A slightly elevated risk was seen among children born in small towns in Denmark, compared with cities or rural areas.

Descriptive statistics of maternal and child health are shown in Table 2. The mothers of Wilms tumor cases were more often of neutral weight compared with control mothers, with none being underweight, and a smaller proportion at the highest weight or BMI. Wilms tumor cases had a threefold increase in the risk of congenital anomalies compared with controls, and were twice as likely to have a 1-minute Apgar score less than 7. The effect estimate for 1-minute Apgar score did not change appreciably after adjustment for presence of a congenital anomaly (OR = 1.86; 95% CI 0.90, 3.82) or for gestational age (OR = 1.93; 95% CI 0.93, 3.99).

In multivariate analyses, Wilms tumor cases were more likely to be high birthweight and LGA, and greater than 55 cm in length at birth (Table 3). We observed smaller placenta size among cases, both before and after adjustment for birthweight (Figure 1). With adjustment for gestational age but not birthweight, results were similar to crude estimates (OR=2.94, 95% CI 1.32-6.56 for placenta size ≤540 g). In sensitivity analyses, the risk of placenta size ≤540 g was slightly attenuated after additional adjustment for maternal age (OR =3.32; 95% CI1.48, 7.47). After stratification by sex, small placentas were seen with both male and female infants, but the effect estimate was higher for females (OR = 5.06; 95% CI 1.59, 16.11, with adjustment for birthweight) than males (OR = 1.88; 95% CI 0.57, 6.18).

When we examined maternal health conditions related to altered placenta size, the sample sizes for specific conditions were generally small, limiting our ability to draw conclusions (Table 4). A slightly larger proportion of case than control mothers had preeclampsia or hypertension, while few cases had gestational or chronic diabetes.

After the exclusion of cases with congenital anomalies (Supplementary Table S3) the risk for Wilms tumor with small placenta increased (adjusted OR = 6.43; 95% CI 1.95, 21.21). Among the cases without anomalies, elevated risk for Wilms was still seen among children at high birthweight (OR=1.53; 95% CI 1.01, 2.31), larger abdominal circumference (OR=1.16; 95% CI 1.00, 1.35, for each 1 cm increase), lower head circumference to abdominal circumference ratio (OR=1.53; 95% CI 1.07, 2.18), and lower placenta-to-birthweight ratio (OR=2.16; 95% CI 1.23, 3.79).

When we stratified by age at diagnosis, we were hampered by small numbers across categories. Nonetheless there was evidence that children diagnosed younger than age 3 had elevated risk for Wilms tumor with lower placenta-to-birthweight ratio (OR = 1.94; 95% CI 1.12, 3.36; Supplementary Table S4) while statistical power was limited to examine many outcomes due to the small number of children (N=100). Children ages 3 and older had more evidence of metrics associated with overgrowth syndromes (Supplementary Table S5), including high birthweight, longer birth length (≥55cm; OR = 2.16; 95% CI 1.19, 3.92), and a larger proportion had a large placenta (≥800 g; 27.6% vs. 14.9% among younger children). However, the older children also had a more sharply increased risk with a small placenta (OR = 9.83; 95% CI 1.94, 49.67).

Discussion

In this population-based study, we observed that Wilms tumor cases were often born with smaller placentas and were more likely to have lower placenta-to-birthweight ratio compared to control children. Effect estimates were higher after the exclusion of cases with congenital anomalies; Beckwith-Wiedemann syndrome occurs with larger placentas.[32-34] Typically, the placenta grows in tandem with the fetus across pregnancy, and at-term placental and fetal weights are positively correlated.[35] Unusually low placenta-to-birthweight ratios are related to a higher risk of stillbirth and other negative perinatal outcomes, such as cerebral palsy.[28,36]

Although we did not have more detailed placental metrics, smaller placenta weight typically indicates a smaller chorionic plate area, allowing for fewer maternal spiral arteries, and a thinner chorionic disk, with a less developed area for villous exchange.[37]

Generally, maternally expressed genes in the placenta lower fetus and placenta size and paternally expressed genes increase both, yet fetal growth is also mediated by changes in placental structure. When fetal weight is much larger than placental weight in Growth Factor Receptor Bound Protein 10 (*Grb10*) knockout mice, the labyrinthine trophoblast, the main surface for maternal-fetal nutrient transfer, accounts for a larger proportion of placental area compared to wild type. Insulin growth factor (*IGF2*) appears to regulate the number, size, and types of cells present in the placenta, and is expressed in all placental tissue, while the *IGF2PO* promoter is exclusive to the labyrinthine trophoblast, and was associated with reduced placenta size relative to the fetus in mice.[38] Placental *IGF2* expression may be mediated by maternal or fetal endocrinology, particularly glucocorticoids which can influence DNA methylation and alter placental nutrient transfer. Whether these processes are altered within the placentas of Wilms tumor cases is unknown, however loss of imprinting of *IGF2*, or aberrant activation of the normally silent maternally inherited allele, is common among PNLR Wilms tumors.[39]

Placental growth is influenced by maternal pre-pregnancy weight, dietary intake in pregnancy, and exercise, perhaps mediated through circulating levels of insulin-like growth factor-1 (IGF-1), leptin, and tumor necrosis factor-α (TNF-α).[40,41] The constituents of diet matter, as higher carbohydrate intake in early pregnancy and low dairy protein intake in late pregnancy both can lower placental weight. However the mother's pre-pregnancy (including early life) nutrient stores may be even more relevant to placenta growth, as they can compensate for poorer pregnancy nutrition.[38,41] There are few studies on maternal nutrition and Wilms tumor risk.

Although we had anthropomorphic information on only a subsample of the mothers in our study, we observed that Wilms tumor mothers were typically of healthy weights, as was reported elsewhere.[42] In contrast, a record-linkage study in New York reported a 41% increase in Wilms with maternal pre-pregnancy weight above 175 lb.[18] Wilms tumor has not been clearly related to gestational weight gain,[17,18,42] although 40+ lbs of weight gain was associated with Wilms diagnosed in children younger than 2 years of age (OR=1.70).[18] Yet it is not possible to assess the importance of gestational weight gain without knowing pre-pregnancy weight and BMI. Interestingly, in two separate locations (US and Ontario) incidence of Wilms decreased after the mid-1990s implementation of programs to fortify cereal grains with folic acid,[43,44] and a German study reported a lower risk with maternal intake of vitamins, iron and/or folate supplements in pregnancy (OR = 0.66).[45] Wilms tumor was also reported in children with spina bifida.[46,47] These findings are intriguing given the important role that folic acid may play in early placental development, as it reportedly increases extravillous trophoblast invasion, matrix metalloproteinase secretion, and angiogenesis.[48]

Smaller placenta size is associated with several risk factors that have been previously reported with Wilms tumor. This study and others reported increases in risk for Wilms with low Apgar scores;[18,49] low Apgar score is also positively associated with small placenta and low placenta-to-birthweight ratio.[50,51] Similarly, meconium staining, pregnancy hypertension, and fetal hydrops have been independently reported with both Wilms tumor and lower placenta weight.[12,18,25,26,51-54] Also notable is the lower mean placenta weight of African-American infants (vs. White),[25] given that Wilms tumor has the highest incidence in African-Americans.[6] However this pattern is not entirely consistent: while maternal diabetes is inversely related to low placenta weight,[26] it has been both positively and negatively associated with Wilms tumor.[18,42,53]

Although placental weight may be a crude proxy for its function, placental size is correlated with birth size, and the ratio between placental weight and birth weight (sometimes called the fetoplacental ratio) may also be an indicator for placental efficiency.[55] However the use of this ratio has also been criticized, both because the average ratio changes across pregnancy, and also because a "normal" ratio can reflect birth weight and placental weight that are both normal, both low, or both high.[50] Wilms tumor cases are typically of higher birthweight,[14] thus in analyses of placenta weight, when we adjusted for birthweight, effect estimates increased. Nonetheless, placenta weight was related to Wilms tumor also in crude analyses, and after adjustment only for gestational age.

Presuming our findings are corroborated elsewhere, it should not be assumed that a smaller placenta is a direct causal agent of Wilms tumor. Placental changes may be secondary to programming within the fetus, or the smaller placenta may be a response to the same insult that caused the cancer. Alternatively, a smaller, weaker placenta may be less able to act as a barrier, allowing the fetus to be exposed to greater levels of xenobiotics or other agents. Other mechanisms are also possible, such as altered placenta secretions including pro-inflammatory cytokines.[56]

With regards to other fetal growth metrics, we corroborated earlier reports of increases in risk with high birthweight and large for gestational age.[12,15-18] While an earlier study found no association with longer birth length,[16] that study examined the risk from lengths ≥54 cm, whereas we found increased risk for Wilms tumor only among children 55 cm or more.

Our study was limited by a lack of information on Wilms tumor subtypes. We lacked detailed information on placenta dimensions which may shed additional light on this association. While adjustment for gestational age might create a collider stratification bias, adjusted findings were similar to crude results. Yet our study adds to the literature on the importance of the placenta in relation to health outcomes,[1] and suggests fetal programming may impact Wilms tumor risk. In combination with the substantial literature on fetal programming and adult health, this suggests a need for larger-scale recording of fetal and placental growth metrics in vital statistics records.

Conflict of Interest statement

The authors declare that there is no conflict of interest.

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TABLE 1 Demographic characteristics of Wilms tumor cases and controls

	Cases (N=217)		Controls (N=4340)		
	Mean (SD)	N (%)	Mean (SD)	N (%)	Crude OR (95% CI)
Maternal age					
Mean (SD)	28.3 (4.8)		28.3 (5.0)		
<25		43 (19.8)		1050 (24.2)	Referent
25-29		91 (41.9)		1584 (36.5)	1.41 (0.97, 2.05)
30-34		58 (26.7)		1165 (26.8)	1.23 (0.81, 1.87)
35-39		22 (10.1)		477 (11.0)	1.14 (0.66, 1.97)
40+		3 (1.4)		64 (1.5)	1.16 (0.34, 3.90)
Paternal age					
Mean (SD)	31.2 (5.9)		31.0 (5.9)		
<25		22 (10.1)		538 (12.5)	Referent
25-29		67 (30.9)		1342 (31.1)	1.23 (0.75, 2.01)
30-34		72 (33.2)		1352 (31.3)	1.31 (0.80, 2.16)
35-39		41 (18.9)		728 (16.9)	1.40 (0.81, 2.40)
40+		15 (6.9)		358 (8.3)	1.04 (0.52, 2.06)
Missing		0		22	
Area of residence at birth					
Urban		65 (30.0)		1454 (33.5)	Referent
Small town		80 (36.9)		1340 (30.9)	1.35 (0.96, 1.89)
Rural		72 (33.2)		1546 (35.6)	1.04 (0.74, 1.47)
Mother's country of birth					
Denmark		206 (94.9)		3973 (91.9)	Referent
Other Europe or N America		6 (2.8)		156 (3.6)	0.74 (0.32, 1.69)
Other		5 (2.3)		196 (4.5)	0.49 (0.20, 1.20)
Missing		0		15	
Father's country of birth					
Denmark		204 (94.4)		3933 (91.3)	Referent
Other Europe or N America		9 (4.2)		153 (3.6)	1.13 (0.57, 2.25)
Other		3 (1.4)		222 (5.2)	0.26 (0.08, 0.81)
Missing		1		32	
Family socioeconomic status (based on job titles)					
Unskilled worker		19 (12.8)		389 (13.7)	0.77 (0.42, 1.42)
Skilled worker		29 (19.5)		488 (17.1)	0.96 (0.55, 1.68)
Low salaried		20 (13.4)		543 (19.1)	0.61 (0.33, 1.10)
High salaried		54 (36.2)		971 (34.1)	0.89 (0.55, 1.44)
Academics and managers		27 (18.1)		455 (16.0)	Referent
Missing		68		1494	
Number of siblings in the household before diagnosis					
0		57 (26.3)		1180 (27.2)	Referent
1		103 (47.5)		2066 (47.6)	1.04 (0.73, 1.46)
2		46 (21.2)		803 (18.5)	1.19 (0.79, 1.80)
3 or more		11 (5.1)		291 (6.7)	0.79 (0.40, 1.53)

TABLE 2 Maternal and child health and risk of Wilms tumor

	Cases (N=217)		Controls (N=4340)		Crude OR (95% CI)
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Maternal Health					
Gravidity [a]					
0		39 (36.1)		793 (36.7)	Referent
1		41 (38.0)		727 (33.7)	1.15 (0.73, 1.81)
2 or more		28 (25.9)		639 (29.6)	0.89 (0.54, 1.46)
Missing		0		1	
Number of previous live births [b]					
0		56 (40.0)		1316 (47.0)	Referent
1		61 (43.6)		1015 (36.3)	1.42 (0.98, 2.05)
2 or more		23 (16.4)		468 (16.7)	1.15 (0.70, 1.89)
Missing		0		1	
Daily smoking at first midwife consultation [c]					
Yes		18 (18.4)		396 (21.7)	0.82 (0.48, 1.40)
No		80 (81.6)		1427 (78.3)	Referent
Missing		4		217	
Cigarettes per day [d]					
Non-smoking		58 (86.6)		1018 (85.8)	Referent
≤ 5		4 (6.0)		43 (3.6)	1.66 (0.57, 4.87)
6-10		4 (6.0)		65 (5.5)	1.07 (0.38, 3.05)
11+		1 (1.5)		60 (5.1)	0.30 (0.04, 2.21)
Risky behavior in pregnancy [e]					
Yes		7 (21.9)		89 (13.9)	1.71 (0.72, 4.05)
No		25 (78.1)		549 (86.1)	Referent
Missing		0		2	
History of miscarriage [f]					
Yes		36 (16.6)		627 (14.5)	1.18 (0.81, 1.72)
No		181 (83.4)		3712 (85.5)	Referent
Missing		0		1	
History of stillbirth [g]					
Yes		2 (1.8)		22 (1.0)	1.82 (0.43, 7.80)
No		110 (98.2)		2217 (99.0)	Referent
Missing		0		1	
Mother's height (cm) [h]	168.8 (7.6)		168.2 (6.6)		
≤163		11 (24.4)		185 (22.4)	Referent
164-168		8 (17.8)		249 (30.2)	0.55 (0.22, 1.39)
169-172		11 (24.4)		179 (21.7)	1.05 (0.44, 2.49)
173+		15 (33.3)		212 (25.7)	1.15 (0.51, 2.60)
Missing		3		135	
Prepregnancy weight (kg) [h]	65.4 (8.5)		68.3 (13.5)		
≤58		10 (22.2)		185 (22.5)	Referent

59-65		14 (31.1)		230 (28.0)	1.13 (0.49, 2.61)
66-74		15 (33.3)		193 (23.5)	1.47 (0.65, 3.36)
75+		6 (13.3)		214 (26.0)	0.52 (0.19, 1.47)
Missing		3		138	
Prepregnancy Body Mass Index (BMI) [h]	23 (3.0)		24.1 (4.5)		
<18.5		0		35 (4.3)	------
18.5-<25		34 (75.6)		509 (62.4)	Referent
25- <30		10 (22.2)		189 (23.2)	0.79 (0.38, 1.64)
30+		1 (2.2)		83 (10.2)	0.19 (0.03, 1.41)
Missing		3		144	
Child Health					
Congenital anomalies [f]					
Yes		63 (29)		483 (11.1)	3.35 (2.46, 4.58)
No		154 (71.0)		3863 (89.0)	Referent
Preterm birth (<37 weeks) [f,i]					
Yes		10 (4.5)		283 (6.3)	0.69 (0.36, 1.32)
No		207 (95.4)		4057 (93.5)	Referent
Missing		7		269	
Apgar score, 1 minute [g]	9.1 (1.8)		9.4 (1.3)		
< 7		9 (8.0)		85 (4.2)	1.99 (0.97, 4.06)
≥ 7		103 (92.0)		1921 (95.8)	Referent
Missing		0		234	
Apgar score, 5 minutes [g]	9.8 (0.9)		9.9 (0.6)		
≤ 9		7 (6.3)		127 (6.3)	0.99 (0.45, 2.19)
10		104 (93.7)		1875 (93.7)	Referent
Missing		1		238	

a. Available for births 1973-1990
b. Available for births 1973-1996
c. Available for births 1991-1996 and 1998+
d. Available for births 1998-2014
e. Available for births 1991-1996
f. Available for births 1973+
g. Available for births 1978-1996
h. Available for births 2004+
i. Shown are the gestational lengths without the use of multiple imputation for missing values.

TABLE 3 Multivariate analysis of growth metrics and Wilms tumor						
	Cases (N=217)		Controls (N=4340)		Crude OR (95% CI)	Adjusted OR (95% CI) [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)		
Placenta weight (g) [b]						
Mean (SD)	648.6 (161.1)		680.6 (168.8)			
≤540		23 (30.3)		243 (18.3)	2.79 (1.25, 6.20)	4.24 (1.84, 9.78)
550-620		17 (22.4)		267 (20.1)	1.83 (0.80, 4.20)	2.07 (0.90, 4.78)
630-690		9 (11.8)		255 (19.2)	Referent	Referent
700-790		12 (15.8)		268 (20.2)	1.30 (0.54, 3.13)	1.13 (0.46, 2.75)
800+		15 (19.7)		293 (22.1)	1.48 (0.64, 3.46)	1.07 (0.44, 2.58)
Missing		1		214		
Birth weight (g)						
Mean (SD)	3454.2 (621.4)		3385.7 (585.7)			
<2500		10 (4.6)		227 (5.5)	0.90 (0.47, 1.74)	1.06 (0.49, 2.29)
2500-4000		160 (73.7)		3321 (79.9)	Referent	Referent
>4000		47 (21.7)		608 (14.6)	1.61 (1.15, 2.26)	1.57 (1.11, 2.22)
Missing		0		184		
Placenta to birth weight ratio [b]						
Per 1 SD decrease					1.92 (1.25, 2.93)	1.81 (1.17, 2.82)
Missing		1		217		
Birth length (cm) [c]						
Mean (SD)	51.9 (2.8)		51.6 (2.7)			
<50cm		28 (13.0)		633 (15.4)	0.88 (0.53, 1.46)	0.95 (0.54, 1.62)
50-51		61 (28.2)		1159 (28.1)	1.05 (0.69, 1.59)	1.06 (0.70, 1.61)
52		38 (17.6)		754 (18.3)	Referent	Referent
53		26 (12.0)		654 (15.9)	0.79 (0.48, 1.32)	0.79 (0.48, 1.32)
54		24 (11.1)		476 (11.6)	1.00 (0.59, 1.70)	1.00 (0.59, 1.69)
55+		39 (18.1)		445 (10.8)	1.76 (1.11, 2.80)	1.74 (1.09, 2.78)
Missing		1		219		
Ponderal index [c]						
Mean (SD)	2.45 (0.32)		2.44 (0.26)			
Smallest		42 (19.4)		859 (20.8)	0.98 (0.62, 1.54)	1.02 (0.64, 1.60)
2nd		43 (19.9)		769 (18.7)	1.12 (0.72, 1.75)	1.13 (0.72, 1.76)
3rd		41 (19.0)		814 (19.8)	Referent	Referent
4th		45 (20.8)		864 (21.0)	1.03 (0.67, 1.60)	1.03 (0.67, 1.59)
Largest		45 (20.8)		815 (19.8)	1.10 (0.71, 1.70)	1.09 (0.71, 1.69)
Missing		1		219		
Head circumference (cm) [b]						
Mean (SD)	35.1 (1.6)		34.9 (2.0)			
≤33		11 (14.9)		265 (19.9)	0.70 (0.33, 1.52)	0.86 (0.39, 1.91)
34		14 (18.9)		257 (19.3)	0.95 (0.47, 1.95)	0.97 (0.47, 1.91)
35		18 (24.3)		311 (23.3)	Referent	Referent
36-37		22 (29.7)		271 (20.3)	1.08 (0.58, 2.01)	1.02 (0.54, 1.91)
38+		5 (6.8)		68 (5.1)	1.30 (0.46, 3.64)	1.24 (0.44, 3.50)
Missing		3		206		
Per 1 cm increase					1.06 (0.94, 1.20)	1.01 (0.87, 1.16)
Abdominal circumference (cm) [b]						

Mean (SD)	33.6 (2.2)		33.1 (2.5)			
≤30		8 (11.1)		184 (14.3)	0.98 (0.37, 2.56)	1.25 (0.46, 3.43)
31-32		12 (16.7)		261 (20.3)	1.10 (0.46, 2.59)	1.16 (0.49, 2.75)
33		10 (13.9)		249 (19.4)	Referent	Referent
34		15 (20.8)		248 (19.3)	1.39 (0.61, 3.15)	1.37 (0.60, 3.12)
35+		27 (37.5)		344 (26.8)	1.86 (0.89, 3.92)	1.79 (0.85, 3.78)
Missing		5		254		
Per 1 cm increase					1.11 (1.00, 1.23)	1.08 (0.96, 1.21)
Head circumference to abdominal circumference ratio [b]						
Per 1 SD decrease					1.23 (0.95, 1.58)	1.18 (0.91, 1.53)
Missing		5		254		
Size for gestational age [d,e]						
<10th percentile		13 (10.2)		231 (9.2)	1.21 (0.67, 2.19)	
Middle 80%		95 (74.2)		2027 (81.1)	Referent	
>90th percentile		20 (15.6)		240 (9.6)	1.79 (1.08, 2.96)	
Missing		0		80		

a. Regressions adjust for gestational age, with the exception of the multivariate analysis of placenta weight, which adjusts for birthweight.

b. Available for births 1997+

c. Available for births 1973+

d. Available for births 1981-2004; analyses include singleton children only.

TABLE 4 Risk of Wilms tumor in relation to maternal health conditions related to small or large placenta size [a]

	Cases (N=194)	Controls (N=3930)	Crude OR (95% CI)
	N (%)	N (%)	
Conditions related to large placenta			
Anemia	7 (3.6)	150 (3.8)	0.94 (0.43, 2.04)
Chronic diabetes	2 (1.0)	42 (1.1)	1.00 (0.24, 4.17)
Gestational diabetes	1 (0.5)	23 (0.6)	0.93 (0.12, 6.95)
Hyperthyroidism	0	27 (0.7)	------
Hypothyroidism	0	21 (0.5)	------
Any of the above	9 (4.6)	226 (5.8)	0.80 (0.40, 1.59)
Conditions related to small placenta			
Preeclampsia	9 (4.6)	155 (3.9)	1.19 (0.60, 2.37)
Chronic hypertension	2 (1.0)	41 (1.0)	1.02 (0.24, 4.24)
Either hypertension or preeclampsia	11 (5.7)	188 (4.8)	1.20 (0.64, 2.25)
Polycystic Ovarian Syndrome	0	12 (0.3)	------
Any of the above	11 (5.7)	200 (5.1)	1.13 (0.60, 2.11)

a. Sample is limited to families where at least one full trimester of the index pregnancy occurred after the establishment of the National Patient Register in 1977. There were no women diagnosed with other conditions previously related to altered placenta size, including: fetal anemia, fetal hydrops, placental thrombi (infarction), toxoplasmosis, syphilis, parvovirus infection, placental tumor.

Supplementary Table 1. Danish extended version of ICD-8 and ICD-10: Codes used to identify conditions related to large placenta

Chronic Diabetes	ICD-10	E10, E100, E100B, E100D, E100E, E100F, E101, E102, E103, E104, E105, E105A, E105B, E105C, E106, E107, E108, E109, E109A, E11, E110, E110D, E110E, E111, E112, E113, E114, E115, E115A, E115B, E115C, E115D, E116, E117, E118, E119, E119A, E120, E121, E122, E123, E124, E125, E127, E128, E129, E13, E130, E131, E132, E133, E134, E135, E135C, E136, E137, E138, E139, E14, E140, E140A, E141, E142, E143, E144, E145, E145B, E145C, E145D, E146, E147, E148, E149, O24, O240, O240A, O240B, O241, O241A, O241B, O241C, O242, O242A, O243, O243A, O243C, O244, O244A, O244B, O244C, O244D, O244E, O249, O249A, O249C
	ICD-8	250, 25000, 250000, 25001, 25002, 25003, 25004, 25005, 25006, 25007, 25008, 25009, 250090, 250091
Gestational diabetes	ICD-10	O244, O244B, O244C, O244D, O244E
Maternal anemia	ICD-10	D46, D460, D460A, D460B, D461, D462, D462A, D462B, D464, D50, D500, D509, D509A, D51, D510, D510A, D511, D513, D519, D52, D520, D521, D529, D530, D532, D539, D550, D551, D552, D559, D589, D59, D590, D592, D599, D599A, D610, D610A, D610C, D611, D612, D613, D619, D619A, D62, D629, D63, D630, D638, D640, D641, D642, D644, D648, D649, O368P, O908, O908B, O908C, O990, O990A, O990B, O990C
	ICD-8	28000, 28001, 28002, 28003, 28008, 28009, 281, 28100, 28101, 28108, 28109, 28119, 28129, 28199, 28209, 28219, 28229, 28239, 28249, 28250, 28258, 28259, 28299, 28309, 28390, 28391, 28392, 28393, 28394, 28395, 28399, 28400, 28402, 28404, 28408, 28409, 28509, 28589, 28599, 63309, 63319, 63399, 67699
Fetal anemia	ICD-10	O368P
Fetal hydrops	ICD-10	O362, O362C, O362D, O362E, P569, P832, P832A, P371A
Placental thrombi (infarction)	ICD-10	O438C
Toxoplasmosis	ICD-10	B580, B582, B582A, B583, B588, B589, P371, P371A
	ICD-8	13009, 13019, 13029, 13099
Placental tumor	ICD-10	C589, C589A, D392
Parvovirus infection	ICD-10	B343
Syphilis	ICD-10	A506, A509, A510, A512, A513A, A514, A519, A521, A523, A528, A529, A530, A539
	ICD-8	9079, 9099, 9109, 9129, 9209, 9299, 9499, 9719, 9799
Hyperthyroidism	ICD-10	E05, E050, E050A, E050B, E050C, E050D, E051, E052, E052A, E053, E054, E055, E058, E058A, E058B, E058C, E059, E059A
	ICD-8	242, 24200, 24201, 24208, 24209, 242090, 24219, 24228, 24229, 242290
Hypothyroidism	ICD-10	E890, E890A, E890B, E029, E03, E030, E030A, E031, E031A, E031C, E032, E033, E034, E035, E038, E039

Supplementary Table 2. Danish extended version of ICD-8 and ICD-10: Codes used to identify conditions related to small placenta

Preeclampsia	ICD-10	O14, O140, O141, O142, O149
	ICD-8	63700, 63702, 63703, 63704, 63709
Hypertension	ICD-10	O13, O139, O169, I10, I109, I11, I110, I119, I119A, I12, I120, I129, I129A, I13, I131, I132, I139, I15, I150, I151, I152, I158, I159
	ICD-8	40009, 40019, 40029, 40039, 40099, 40199, 40299, 40399, 40499
Hypertension or preeclampsia	ICD-10	O13, O139, O14, O140, O141, O142, O149, O169, I10, I109, I11, I110, I119, I119A, I12, I120, I129, I129A, I13, I131, I132, I139, I15, I150, I151, I152, I158, I159
	ICD-8	40009, 40019, 40029, 40039, 40099, 40199, 40299, 40399, 40499, 63700, 63702, 63703, 63704, 63709
Polycystic ovarian syndrome	ICD-10	E282, E282B, E282C

Supplementary Table 3. Fetal and Placental Growth Metrics, among Children without Congenital Anomalies						
	Cases (N=154)		Controls (N=3863)		Crude OR (95% CI)	Adjusted OR (95% CI) [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)		
Placenta weight (g) [b]						
Mean (SD)	652.2 (161.0)		684.7 (163.2)			
≤540		13 (28.3)		198 (17.1)	3.58 (1.13, 11.37)	6.43 (1.95, 21.21)
550-620		11 (23.9)		228 (19.7)	3.07 (0.95, 9.98)	3.84 (1.17, 12.6)
630-690		4 (8.7)		226 (19.6)	Referent	Referent
700-790		9 (19.6)		244 (21.1)	2.05 (0.62, 6.82)	1.85 (0.55, 6.19)
800+		9 (19.6)		260 (22.5)	1.94 (0.58, 6.43)	1.31 (0.38, 4.54)
Missing		1		188		
Birth weight (g)						
Mean (SD)	3442.2 (625.5)		3397.3 (575.8)			
<2500		8 (5.2)		178 (4.8)	1.09 (0.52, 2.27)	1.40 (0.58, 3.35)
2500-4000		113 (73.4)		2967 (80.2)	Referent	Referent
>4000		33 (21.4)		555 (15.0)	1.59 (1.06, 2.39)	1.53 (1.01, 2.31)
Missing		0		163		
Placenta to birth weight ratio [b]						
Per 1 SD decrease					2.22 (1.28, 3.83)	2.16 (1.23, 3.79)
Missing		1		191		
Birth length (cm) [c]						
Mean (SD)	52.1 (2.7)		51.7 (2.6)			
<50cm		19 (12.4)		538 (14.7)	0.65 (0.36, 1.17)	0.67 (0.36, 1.26)
50-51		38 (24.8)		1034 (28.2)	0.70 (0.43, 1.13)	0.70 (0.43, 1.14)
52		34 (22.2)		671 (18.3)	Referent	Referent
53		16 (10.5)		596 (16.2)	0.52 (0.28, 0.97)	0.52 (0.28, 0.97)
54		15 (9.8)		436 (11.9)	0.66 (0.35, 1.25)	0.66 (0.35, 1.24)
55+		31 (20.3)		395 (10.8)	1.56 (0.93, 2.62)	1.56 (0.93, 2.61)
Missing		1		193		
Ponderal index [c]						
Mean (SD)	2.42 (0.26)		2.44 (0.25)			
Smallest		34 (22.2)		756 (20.6)	1.15 (0.68, 1.95)	1.19 (0.70, 2.03)
2nd		31 (20.3)		677 (18.4)	1.24 (0.73, 2.12)	1.25 (0.73, 2.13)
3rd		28 (18.3)		725 (19.8)	Referent	Referent
4th		30 (19.6)		787 (21.4)	0.98 (0.58, 1.67)	0.98 (0.58, 1.67)
Largest		30 (19.6)		725 (19.8)	1.13 (0.66, 1.93)	1.12 (0.66, 1.91)
Missing		1		193		
Head circumference (cm) [b]						
Mean (SD)	35.0 (1.6)		34.9 (1.9)			
≤33		7 (15.6)		222 (19.1)	0.72 (0.27, 1.89)	0.87 (0.32, 2.36)
34		7 (15.6)		221 (19.0)	0.79 (0.30, 2.08)	0.78 (0.30, 2.06)
35		11 (24.4)		277 (23.8)	Referent	Referent
36-37		18 (40.0)		389 (33.4)	1.12 (0.52, 2.43)	1.05 (0.48, 2.30)
38+		2 (4.4)		56 (4.8)	0.82 (0.17, 3.96)	---------
Missing		2		179		
Per 1cm increase					1.05 (0.89, 1.24)	0.99 (0.82, 1.19)
Abdominal circumference (cm) [b]						
Mean (SD)	33.9 (2.1)		33.1 (2.4)			
≤30		3 (7)		147 (13.0)	0.49 (0.12, 1.95)	---------
31-32		7 (16.3)		228 (20.2)	0.94 (0.32, 2.77)	0.97 (0.33, 2.87)
33		7 (16.3)		228 (20.2)	Referent	Referent
34		8 (18.6)		227 (20.1)	1.05 (0.37, 2.97)	1.06 (0.37, 3.00)

35+	18 (41.9)	299 (26.5)	1.77 (0.72, 4.35)	1.71 (0.69, 4.22)
Missing	4	215		
Per 1 cm increase			1.19 (1.04, 1.37)	1.16 (1.00, 1.35)
Head circumference to abdominal circumference ratio [b]				
Per 1 SD decrease			1.58 (1.12, 2.23)	1.53 (1.07, 2.18)
Missing	4	215		
Size for gestational age [d]				
<10th percentile	9 (10.6)	200 (8.9)	1.10 (0.54, 2.25)	
Middle 80%	64 (75.3)	1826 (81.6)	Referent	
>90th percentile	12 (14.1)	213 (9.5)	1.56 (0.81, 2.97)	
Missing	0	71		

a. Regressions adjust for gestational age, with the exception of the multivariate analysis of placenta weight, which adjusts for birthweight.
b. Available for births 1997+
c. Available for births 1973+
d. Available 1981-2004, singleton pregnancies only

Supplementary Table 4. Fetal and Placental Growth Metrics among Children Diagnosed ages ≤ 2 years						
	Cases (N=100)		Controls (N=2000)		Crude OR (95% CI)	Adjusted OR (95% CI) [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)		
Placenta weight (g) [b]						
Mean (SD)	652.2 (161.0)		684.7 (163.2)			
≤540		14 (29.8)		153 (18.7)	1.99 (0.77, 5.11)	2.78 (1.03, 7.53)
550-620		11 (23.4)		163 (19.9)	1.48 (0.55, 3.97)	1.61 (0.60, 4.33)
630-690		7 (14.9)		148 (18.1)	Referent	Referent
700-790		8 (17.0)		169 (20.7)	1.01 (0.36, 2.85)	0.89 (0.31, 2.55)
800+		7 (14.9)		185 (22.6)	0.82 (0.28, 2.38)	0.63 (0.21, 1.94)
Missing		0		122		
Birth weight (g)						
Mean (SD)	3442.2 (625.5)		3397.3 (575.8)			
<2500		3 (3.0)		103 (5.4)	0.53 (0.17, 1.72)	-----
2500-4000		82 (82.0)		1499 (79.1)	Referent	Referent
>4000		15 (15.0)		294 (15.5)	0.93 (0.53, 1.64)	0.95 (0.53, 1.68)
Missing		0		104		
Placenta to birth weight ratio [b]						
Per 1 SD decrease					1.94 (1.13, 3.33)	1.94 (1.12, 3.36)
Missing		0		125		
Birth length (cm) [c]						
Mean (SD)	52.1 (2.7)		51.7 (2.6)			
<50cm		11 (11.1)		287 (15.3)	0.82 (0.38, 1.79)	0.79 (0.34, 1.86)
50-51		35 (35.4)		526 (28.0)	1.42 (0.78, 2.58)	1.41 (0.77, 2.57)
52		17 (17.2)		357 (19.0)	Referent	Referent
53		14 (14.1)		295 (15.7)	0.99 (0.48, 2.04)	0.99 (0.48, 2.05)
54		11 (11.1)		212 (11.3)	1.09 (0.50, 2.37)	1.09 (0.50, 2.37)
55+		11 (11.1)		203 (10.8)	1.16 (0.53, 2.53)	1.16 (0.53, 2.54)
Missing		1		120		
Ponderal index [c]						
Mean (SD)	2.4 (0.3)		2.4 (0.3)			
Smallest		15 (15.2)		315 (16.8)	0.79 (0.41, 1.56)	0.80 (0.40, 1.58)
2nd		15 (15.2)		329 (17.5)	0.76 (0.39, 1.49)	0.76 (0.39, 1.49)
3rd		23 (23.2)		379 (20.2)	Referent	Referent
4th		24 (24.2)		427 (22.7)	0.93 (0.51, 1.67)	0.93 (0.51, 1.67)
Largest		22 (22.2)		430 (22.9)	0.84 (0.46, 1.54)	0.84 (0.46, 1.54)
Missing		1		120		
Head circumference (cm) [b]						
Mean (SD)	35.0 (1.6)		34.9 (1.9)			
≤33		5 (11.1)		169 (20.5)	0.39 (0.14, 1.12)	--------
34		9 (20.0)		154 (18.7)	0.81 (0.34, 1.92)	0.82 (0.35, 1.93)
35		14 (31.1)		188 (22.8)	Referent	Referent
36-37		16 (35.6)		280 (33.9)	0.79 (0.37, 1.67)	0.78 (0.37, 1.66)
38+		1 (2.2)		34 (4.1)	0.41 (0.05, 3.19)	--------
Missing		2		115		
Per 1cm increase					1.06 (0.92, 1.23)	1.05 (0.89, 1.23)
Abdominal circumference (cm) [b]						
Mean (SD)	33.9 (2.1)		33.1 (2.4)			
≤30		6 (14.0)		108 (13.5)	1.27 (0.39, 4.14)	1.50 (0.44, 5.20)
31-32		8 (18.6)		163 (20.3)	1.24 (0.42, 3.67)	1.29 (0.43, 3.86)
33		6 (14.0)		157 (19.6)	Referent	Referent
34		11 (25.6)		155 (19.3)	1.70 (0.61, 4.75)	1.67 (0.60, 4.68)

35+	12 (27.9)	219 (27.3)	1.35 (0.50, 3.67)	1.32 (0.49, 3.60)
Missing	4	138		
Per 1 cm increase			1.04 (0.91, 1.18)	1.02 (0.88, 1.18)
Head circumference to abdominal circumference ratio [b]				
Per 1 SD decrease			1.02 (0.76, 1.39)	0.99 (0.72, 1.36)
Missing	4	138		
Size for gestational age [d]				
<10th percentile	7 (10.9)	109 (8.8)	1.28 (0.57, 2.90)	
Middle 80%	50 (78.1)	1005 (81.5)	Referent	
>90th percentile	7 (10.9)	119 (9.7)	1.18 (0.52, 2.66)	
Missing	0	48		

a. Regressions adjust for gestational age, with the exception of the multivariate analysis of placenta weight,
b. Available for births 1997+
c. Available for births 1973+
d. Available 1981-2004, singleton pregnancies only

Supplementary Table 5. Fetal and Placental Growth Metrics among Children Diagnosed Ages 3+						
	Cases (N=117)		Controls (N=2340)		Crude OR (95% CI)	Adjusted OR (95% CI) [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)		
Placenta weight (g) [b]						
Mean (SD)	652.2 (161.0)		684.7			
≤540		9 (31.0)		90 (17.7)	5.81 (1.19, 28.26)	9.83 (1.94, 49.67)
550-620		6 (20.7)		104 (20.5)	3.05 (0.60, 15.41)	3.68 (0.72, 18.93)
630-690		2 (6.9)		107 (21.1)	Referent	Referent
700-790		4 (13.8)		99 (19.5)	2.32 (0.41, 13.03)	----
800+		8 (27.6)		108 (21.3)	4.18 (0.85, 20.41)	2.70 (0.53, 13.69)
Missing		1		92		
Birth weight (g)						
Mean (SD)	3442.2		3397.3			
<2500		7 (6.0)		124 (5.5)	1.27 (0.58, 2.82)	1.84 (0.72, 4.73)
2500-4000		78 (66.7)		1822 (80.6)	Referent	Referent
>4000		32 (27.4)		314 (13.9)	2.41 (1.56, 3.71)	2.26 (1.45, 3.52)
Missing		0		80		
Placenta-birth weight ratio [b]						
Per 1 SD decrease					1.87 (0.94, 3.72)	1.56 (0.76, 3.20)
Missing		1		92		
Birth length (cm) [c]						
Mean (SD)	52.1 (2.7)		51.7 (2.6)			
<50cm		17 (14.5)		346 (15.4)	0.93 (0.48, 1.79)	1.06 (0.52, 2.17)
50-51		26 (22.2)		633 (28.2)	0.77 (0.42, 1.39)	0.79 (0.44, 1.43)
52		21 (17.9)		397 (17.7)	Referent	Referent
53		12 (10.3)		359 (16.0)	0.63 (0.31, 1.31)	0.63 (0.31, 1.30)
54		13 (11.1)		264 (11.8)	0.95 (0.46, 1.93)	0.93 (0.45, 1.90)
55+		28 (23.9)		242 (10.8)	2.22 (1.22, 4.02)	2.16 (1.19, 3.92)
Missing		0		99		
Ponderal index [c]						
Mean (SD)	2.43 (0.38)		2.41 (0.26)			
Smallest		27 (23.1)		544 (24.3)	1.22 (0.65, 2.28)	1.28 (0.68, 2.41)
2nd		28 (23.9)		440 (19.6)	1.55 (0.84, 2.87)	1.56 (0.85, 2.88)
3rd		18 (15.4)		435 (19.4)	Referent	Referent
4th		21 (17.9)		437 (19.5)	1.16 (0.61, 2.21)	1.14 (0.60, 2.18)
Largest		23 (19.7)		385 (17.2)	1.44 (0.76, 2.72)	1.43 (0.76, 2.70)
Missing		0		99		
Head circumference (cm) [b]						
Mean (SD)	35.0 (1.6)		34.9 (1.9)			
≤33		6 (20.7)		96 (18.9)	1.79 (0.49, 6.51)	2.74 (0.74, 10.22)
34		5 (17.2)		103 (20.2)	1.42 (0.37, 5.44)	1.47 (0.38, 5.67)
35		4 (13.8)		123 (24.2)	Referent	Referent
36-37		10 (34.5)		153 (30.1)	2.08 (0.63, 6.83)	1.73 (0.53, 5.72)
38+		4 (13.8)		34 (6.7)	3.71 (0.87, 15.84)	-----
Missing		1		91		
Per 1cm increase					1.06 (0.86, 1.32)	0.94 (0.73, 1.22)
Abdominal circumference (cm) [b]						
Mean (SD)	33.9 (2.1)		33.1 (2.4)			
≤32		6 (20.7)		174 (36.0)	0.80 (0.27, 2.39)	0.95 (0.31, 2.88)
33-34		8 (27.6)		185 (38.2)	Referent	Referent
35+		15 (51.7)		125 (25.8)	2.83 (1.16, 6.92)	2.61 (1.05, 6.45)
Missing		1		116		

Per 1 cm increase			1.23 (1.03, 1.46)	1.18 (0.98, 1.43)
Head circumference-abdominal circumference ratio [b]				
Per 1 SD decrease			1.66 (1.09, 2.54)	1.60 (1.03, 2.50)
Missing	1	116		
Size for gestational age [d]				
<10th percentile	6 (9.4)	122 (9.6)	1.13 (0.47, 2.70)	
Middle 80%	45 (70.3)	1022 (80.8)	Referent	
>90th percentile	13 (20.3)	121 (9.6)	2.49 (1.30, 4.77)	
Missing	0	32		

a. Regressions adjust for gestational age, with the exception of the multivariate analysis of placenta weight, which adjusts for birthweight.

b. Available for births 1997+

c. Available for births 1973+

d. Available 1981-2004, singleton pregnancies only

Supplementary Table 6. Multivariate analysis of growth metrics and Wilms tumor, among women whose gestational age was not imputed

	Cases (N=210)		Controls (N=4071)		Crude OR (95% CI)	Adjusted OR (95% CI) [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)		
Placenta weight (g) [b]						
Mean (SD)	648.6 (161.1)		680.6 (168.8)			
≤540		23 (31.1)		241 (18.3)	2.79 (1.25, 6.21)	4.44 (1.93, 10.25)
550-620		16 (21.6)		265 (20.1)	1.72 (0.74, 3.98)	1.95 (0.84, 4.55)
630-690		9 (12.2)		255 (19.3)	Referent	Referent
700-790		11 (14.9)		267 (20.3)	1.17 (0.48, 2.88)	0.99 (0.40, 2.46)
800+		15 (20.3)		290 (22.0)	1.50 (0.64, 3.50)	1.03 (0.42, 2.50)
Missing		1		44		
Birth weight (g)						
Mean (SD)	3454.2 (621.4)		3385.7 (585.7)			
<2500		9 (4.3)		223 (5.5)	0.83 (0.42, 1.64)	0.97 (0.43, 2.17)
2500-4000		156 (74.3)		3239 (79.8)	Referent	Referent
>4000		45 (21.4)		597 (14.7)	1.59 (1.13, 2.25)	1.55 (1.09, 2.21)
Missing		0		12		
Placenta to birth weight ratio [b]						
Per 1 SD decrease					2.07 (1.33, 3.22)	1.94 (1.23, 3.08)
Missing		1		47		
Birth length (cm) [c]						
Mean (SD)	51.9 (2.8)		51.6 (2.7)			
<50cm		27 (12.9)		623 (15.5)	0.87 (0.52, 1.46)	0.95 (0.54, 1.66)
50-51		61 (29.2)		1134 (28.2)	1.08 (0.71, 1.65)	1.10 (0.72, 1.69)
52		37 (17.7)		733 (18.2)	Referent	Referent
53		24 (11.5)		640 (15.9)	0.76 (0.45, 1.28)	0.76 (0.45, 1.28)
54		22 (10.5)		462 (11.5)	0.95 (0.55, 1.63)	0.94 (0.55, 1.62)
55+		38 (18.2)		434 (10.8)	1.80 (1.13, 2.89)	1.78 (1.11, 2.85)
Missing		1		45		
Ponderal index [c]						
Mean (SD)	2.4 (0.3)		2.4 (0.3)			
Smallest		42 (20.1)		838 (20.8)	0.98 (0.62, 1.55)	1.02 (0.65, 1.62)
2nd		39 (18.7)		749 (18.6)	1.02 (0.65, 1.61)	1.03 (0.65, 1.62)
3rd		41 (19.6)		794 (19.7)	Referent	Referent
4th		44 (21.1)		843 (20.9)	1.01 (0.65, 1.57)	1.01 (0.65, 1.57)
Largest		43 (20.6)		802 (19.9)	1.06 (0.68, 1.64)	1.05 (0.68, 1.64)
Missing		1		45		
Head circumference (cm) [b]						
Mean (SD)	35.1 (1.6)		34.9 (2.0)			
≤33		11 (15.3)		264 (19.9)	0.74 (0.34, 1.62)	0.95 (0.43, 2.11)
34		14 (19.4)		257 (19.4)	0.99 (0.48, 2.06)	1.02 (0.49, 2.11)
35		17 (23.6)		310 (23.4)	Referent	Referent
36-37		25 (34.7)		427 (32.2)	1.11 (0.58, 2.10)	1.03 (0.54, 1.97)
38+		5 (6.9)		68 (5.1)	1.40 (0.50, 3.97)	1.33 (0.47, 3.80)
Missing		3		36		
Per 1 cm increase					1.06 (0.94, 1.12)	1.00 (0.86, 1.16)
Abdominal circumference (cm) [b]						
Mean (SD)	33.6 (2.2)		33.1 (2.5)			
≤30		8 (11.3)		184 (14.4)	0.98 (0.37, 2.56)	1.25 (0.46, 3.40)
31-32		12 (16.9)		260 (20.3)	1.10 (0.46, 2.59)	1.16 (0.49, 2.74)
33		10 (14.1)		247 (19.3)	Referent	Referent

34	14 (19.7)	245 (19.2)	1.30 (0.57, 3.00)	1.30 (0.56, 2.99)
35+	27 (38.0)	342 (26.8)	1.87 (0.89, 3.94)	1.81 (0.86, 3.81)
Missing	4	84		
Per 1 cm increase			1.11 (1.00, 1.23)	1.08 (0.96, 1.21)
Head circumference to abdominal circumference ratio [b]				
Per 1 SD decrease			1.23 (0.96, 1.60)	1.19 (0.91, 1.56)
Missing	4	84		
Size for gestational age [d]				
<10th percentile	13 (10.3)	231 (9.3)	1.22 (0.67, 2.21)	
Middle 80%	93 (73.8)	2002 (81.0)	Referent	
>90th percentile	20 (15.9)	240 (9.7)	1.81 (1.10, 3.00)	
Missing	0	3		

a. Regressions adjust for gestational age, with the exception of the multivariate analysis of placenta weight, which adjusts for birthweight.

b. Available for births 1997+

c. Available for births 1973+

d. Available 1981-2004, singleton pregnancies only

FIGURE 1 Birth weight vs. Placenta weight, Wilms tumor cases and controls