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Crump, Casey; Sundquist, Jan; Sieh, Weiva; Winkleby, Marilyn A.; Sundquist, Kristina

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Total number of authors:
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LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

PERINATAL RISK FACTORS FOR WILMS TUMOR IN A SWEDISH NATIONAL COHORT

Authors:

1. Casey Crump, M.D., Ph.D. (Corresponding Author), Stanford University, Department of Medicine, 211 Quarry Road, Suite 405, MC 5985, Palo Alto, California 94304-1426, USA. Tel: (650) 723-6963. Fax: (650) 498-7750. Email: kccrump@stanford.edu
2. Jan Sundquist, M.D., Ph.D., Lund University, Center for Primary Health Care Research, Clinical Research Centre (CRC), building 28, floor 11, Jan Waldenströms gata 35, Skåne University Hospital, SE-205 02 Malmö, Sweden
3. Weiva Sieh, M.D., Ph.D., Stanford University, Department of Health Research and Policy, HRP Redwood Building, T254B, Stanford, California 94305-5405, USA
4. Marilyn A. Winkleby, Ph.D., Stanford University, Stanford Prevention Research Center, Medical School Office Building, 251 Campus Drive, Room X318, Stanford, California 94305-5411, USA
5. Kristina Sundquist, M.D., Ph.D., Lund University, Center for Primary Health Care Research, Clinical Research Centre (CRC), building 28, floor 11, Jan Waldenströms gata 35, Skåne University Hospital, SE-205 02 Malmö, Sweden

Running title: Risk Factors for Wilms Tumor

Abbreviations: CI (confidence interval), aHR (adjusted hazard ratio), aOR (adjusted odds ratio), IGF2 (insulin-like growth factor 2), SD (standard deviation), WT1 (Wilms tumor 1)

ABSTRACT

Background: Perinatal risk factors including high birth weight have been associated with Wilms tumor in case-control studies. However, these findings have seldom been examined in large cohort studies, and the specific contributions of gestational age at birth and fetal growth remain unknown.

Methods: We conducted the largest population-based cohort study to date consisting of 3,571,574 persons born in Sweden in 1973-2008, followed up for Wilms tumor incidence through 2009 to examine perinatal risk factors.

Results: There were 443 Wilms tumor cases identified in 66.3 million person-years of follow-up. After adjusting for gestational age and other perinatal factors, high fetal growth was associated with increased risk of Wilms tumor among girls (hazard ratio per 1 standard deviation [SD], 1.36; 95% CI, 1.20-1.54; $P<0.001$), but not boys (1.10; 95% CI, 0.97-1.25; $P=0.14$) ($P_{interaction}=0.02$). Among girls, high fetal growth was associated with disease onset before age 5 years (odds ratio per 1 SD, 1.47; 95% CI, 1.28-1.69; $P<0.001$), but not beyond (1.00; 95% CI, 0.76-1.31; $P=0.99$). No clear associations were found for gestational age at birth or other perinatal factors.

Conclusion: In this large cohort study, high fetal growth was associated with Wilms tumor before age 5 years among girls. These findings suggest that early-life growth factor pathways for Wilms tumor may be more common among girls than boys. Further elucidation of these mechanisms may reveal better targets for prevention or treatment of specific subtypes of Wilms tumor.

Key words: fetal development; gestational age; risk factors; Wilms tumor

INTRODUCTION

Wilms tumor, or nephroblastoma, comprises ~95% of all kidney cancers among children <15 years of age.[1] Known susceptibility genes and overgrowth disorders such as Beckwith-Wiedemann syndrome account for only a minority of cases,[1] whereas in most cases the cause is unknown. Because most Wilms tumors are diagnosed in the first few years of life, other perinatal factors may be etiologically important, and their identification may provide insights into mechanisms. Recent case-control studies[2-4] and a large review based predominantly on case-control data[1] have reported that high birth weight is associated with Wilms tumor, possibly through growth factor pathways involving insulin-like growth factor 2 (IGF2).[5-7] However, most studies to date have focused on birth weight without examining its specific components—gestational age at birth and fetal growth—hence the specific contributions of these factors are still unclear. Preterm birth and low birth order have also been associated with Wilms tumor but have been less widely studied.[1] These issues have not been examined in large population-based cohort studies, which have the potential to provide more robust and generalizable risk estimates and to clarify susceptible population subgroups. Such studies can improve our understanding of etiologic pathways and ultimately may help identify better targets for preventive or therapeutic interventions.

We conducted the largest population-based cohort study to date to examine perinatal risk factors for Wilms tumor among ~3.5 million children born in Sweden during 1973-2008. Detailed information on perinatal factors and Wilms tumor incidence were obtained from birth and cancer registries that are nearly 100% complete nationwide. Our aims were to examine whether fetal growth, gestational age at birth, and other perinatal factors are associated with Wilms tumor in a large national cohort.

MATERIALS AND METHODS

Study population

We identified 3,595,055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. We excluded 10,438 (0.3%) individuals who had missing information for birth weight, and 7,704 (0.2%) others who had missing information for gestational age at birth. To remove possible coding errors, we also excluded 5,339 (0.1%) others who had a reported birth weight more than four standard deviations above or below the mean birth weight for gestational age and sex based on a Swedish reference growth curve.[8] A total of 3,571,574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Wilms tumor ascertainment

The study cohort was followed up for incidence of Wilms tumor from birth through December 31, 2009. All Wilms tumors were identified from the Swedish Cancer Registry, which includes all primary incident cancers in Sweden since 1958 with compulsory reporting nationwide. Wilms tumors were classified using the *International Classification of Diseases, 7th revision* (*ICD-7*) code 180, and Systemized Nomenclature of Medicine (SNOMED) code 8960 since 1993 or synonymous definitions provided by the World Health Organization prior to this period.[9]

Perinatal variables

Perinatal and sociodemographic characteristics were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number.[10] The following were examined as predictors of interest or adjustment variables: sex; age (continuous); birth year (1973-1979, 1980-1989, 1990-1999, 2000-2008); fetal growth (measured using a standardized fetal growth variable, defined as the number of standard deviations [SD] from the mean birth weight for gestational age and sex based on a Swedish reference growth curve,[8] and modeled as a continuous variable or categorized into four groups [<-1; -1 to <1; 1 to <2; ≥2 SD] to allow for a non-linear effect; small numbers of cases prevented further stratification into additional groups); gestational age at birth (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled as a continuous variable or categorized into three groups [<37, 37-41, ≥42 completed weeks] to allow for a non-linear effect); multiple birth (singleton vs. twin or higher order); birth order (1, 2, ≥3); maternal and paternal age at birth (<25, 25-29, 30-34, ≥35 years); maternal and paternal education level (compulsory high school or less [≤9 years], practical high school or some theoretical high school [10-11 years], theoretical high school and/or some college [12-14 years], college and/or post-graduate study [≥15 years]); and family history of Wilms tumor in a parent or sibling (yes or no; identified from the Swedish Cancer Registry from 1958 through 2009).

As an alternative to the standardized fetal growth variable, we also examined birth weight (modeled as a continuous or categorical [<2500, 2500-3999, ≥4000 g] variable) and birth length (crown-heel length in cm, modeled as a continuous or categorical [<48, 48-52, ≥53 cm] variable) in separate analyses.

Statistical analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between perinatal characteristics and incidence of Wilms tumor. Age was used as the Cox model time scale. Individuals were censored at death (n=32,493; 0.9%) or at emigration as determined by the absence of a Swedish residential address in census data (n=102,212; 2.9%). Analyses were conducted first unadjusted and then adjusted for covariates (as above). First-order interactions among the covariates were explored using a likelihood ratio test. All analyses were subsequently stratified by sex because of significant differences in risk estimates. The proportional hazards assumption was assessed using the method described by Grambsch and Therneau[11] and was met in each of the models. In addition, multinomial logistic regression was used to test for heterogeneity in the association between perinatal risk factors and Wilms tumor by age at diagnosis, examining different age cutpoints. All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 13.0.[12]

RESULTS

Among the 3,571,574 individuals in this cohort, 443 Wilms tumor cases (224 girls and 219 boys) were identified in 66.3 million person-years of follow-up. The overall incidence rate per 1 million person-years was 6.7 (7.0 for girls and 6.4 for boys). The mean age at diagnosis was 3.8 years overall (SD 4.0; median 2.8), 3.9 years among girls (SD 3.9; median 3.0), and 3.6 years among boys (SD 4.0; median 2.4). Table 1 shows perinatal characteristics by Wilms tumor diagnosis, stratified by sex. High fetal growth appeared more common among girls diagnosed with Wilms tumor than those who were not; whereas only modest differences in fetal growth

were seen among boys. Beckwith-Wiedemann syndrome (an overgrowth syndrome known to predispose to Wilms tumor) and a family history of Wilms tumor were proportionately more common among children diagnosed with Wilms tumor but were identified in only 8 and 3 cases, respectively (Table 1).

High fetal growth was associated with a significantly increased risk of Wilms tumor in the overall cohort (adjusted hazard ratio [aHR] per additional 1 SD of fetal growth, 1.23; 95% CI, 1.12-1.34; $P<0.001$; not shown in the tables). However, this was mainly driven by an association among girls (aHR per additional 1 SD of fetal growth, 1.36; 95% CI, 1.20-1.54; $P<0.001$), whereas no clear association was found among boys (aHR per additional 1 SD of fetal growth, 1.10; 95% CI, 0.97-1.25; $P=0.14$). These sex-specific risk estimates differed significantly from each other ($P_{interaction}=0.02$). As a result, all subsequent analyses were stratified by sex.

After adjusting for gestational age at birth and other covariates, high fetal growth was a strong risk factor for Wilms tumor only among girls (Table 2). Girls with highest fetal growth (≥2 SD above the mean) had a 3-fold risk of Wilms tumor relative to those at -1 to 1 SD (aHR, 3.65; 95% CI, 2.31-5.77; $P<0.001$). This association among girls was limited to disease onset before age 5 years (adjusted odds ratio [aOR] per additional 1 SD of fetal growth, 1.47; 95% CI, 1.28-1.69; $P<0.001$; based on 175 cases), and not beyond (aOR per additional 1 SD of fetal growth, 1.00; 95% CI, 0.76-1.31; $P=0.99$; based on 49 cases) ($P=0.01$ for heterogeneity in aORs comparing <5 vs. ≥5 years). Earlier age cutpoints were explored but risk estimates for earlier- vs. later-onset did not vary significantly using cutpoints <5 years. Birth weight and birth length, examined in separate models, were similarly associated with increased risk of Wilms tumor

among girls (aHR per additional 1000 g of birth weight, 1.95; 95% CI, 1.49-2.56; $P<0.001$; aHR per additional 1 cm of birth length, 1.14; 95% CI, 1.07-1.22; $P<0.001$).

In contrast, fetal growth was not significantly associated with Wilms tumor among boys (Table 2). Boys with birth weight ≥4000 g had a modestly increased risk of Wilms tumor relative to those with birth weight 2500-3999 g (aHR, 1.44; 95% CI, 1.06-1.96, $P=0.02$); but unlike among girls, there was no linear trend across the full range of birth weight (Table 2). Adjusting for any combination of covariates had little effect on risk estimates compared with unadjusted estimates (data not shown). Exclusion of children diagnosed with Beckwith-Wiedemann syndrome (n=193) also had little effect on any of these results (data not shown).

Beckwith-Wiedemann syndrome and family history of Wilms tumor were not sufficiently common among cases to obtain stable risk estimates. No other perinatal variables were clearly associated with Wilms tumor. One paternal education category was statistically significant but the pattern was not consistent across the full range of education levels (Table 2). Preterm birth (gestational age <37 completed weeks) was associated with a near-significant increased risk of Wilms tumor among girls (aHR, 1.61; 95% CI, 0.98-2.65; $P=0.06$), but not among boys. Except for the interaction between sex and fetal growth ($P_{interaction}=0.02$, described above), no interactions among other covariates were found with respect to Wilms tumor risk.

DISCUSSION

In this large national cohort study, high fetal growth was associated with increased risk of Wilms tumor with onset before age 5 years among girls, but not later-onset Wilms tumor or among boys. No clear associations were found for gestational age at birth, birth order, parental

age, or other perinatal factors. These findings suggest that early-life growth factor pathways for Wilms tumor may be more common among girls than boys.

Although few studies have examined sex-specific risk estimates, three case-control studies from Nordic countries have suggested an association between high birth weight and Wilms tumor among girls only. A case-control study of 690 Wilms tumor cases and 3,298 controls from Denmark, Finland, Norway, and Sweden reported that the relative odds of Wilms tumor per 500 g greater birth weight were 1.28 (95% CI, 1.15-1.42) among girls and 1.01 (95% CI, 0.91-1.12) among boys, and found no differences by age at diagnosis.[2] A larger case-control study (961 cases) with overlapping data from the same countries reported a similar stronger association with high birth weight among girls,[3] as did a smaller Danish case-control study (126 cases).[13] A meta-analysis of 37 studies, including 12 that examined high birth weight, reported that the overall relative odds of Wilms tumor for high vs. normal birth weight was 1.36 (95% CI, 1.12-1.64), but did not report sex-specific results.[1] We further examined these relationships in the largest population-based cohort study to date. Our findings confirm a link between high fetal growth and Wilms tumor among girls, and suggest that this was limited to disease onset before age 5 years. High fetal growth may be a catalyst[14] for Wilms tumor among girls, although the underlying mechanisms are still not well established. Our results appear consistent with previously reported associations between high birth weight and Wilms tumor only among children with perilobar nephrogenic rests (precursor lesions consisting of embryonic renal cells that persist into childhood), which were more common among girls.[6, 15] It has been hypothesized that one type of Wilms tumor is characterized by perilobar nephrogenic rests and altered expression of the IGF2 gene, which is located on the short end of chromosome 11 near the Wilms tumor 1 (WT1) gene.[5-6] Perilobar nephrogenic rests may result from

excessive exposure of nephrogenic blastema to IGF2 during the period of nephron formation.[2, 5-6] This process may be more common among girls[6, 15] and, also consistent with our findings, has been associated with an earlier age of onset than Wilms tumors without nephrogenic rests.[6] Studies with access to information on nephrogenic rests and epigenetic studies of IGF polymorphisms may help further delineate these mechanisms.

The main strength of the current study was its large population-based cohort design, which enabled well-powered analyses while avoiding selection bias that may potentially occur in case-control studies. Linkage of national birth and cancer registries provided nearly 100% nationwide ascertainment of perinatal factors and Wilms tumor,[16-17] and prevented bias that may result from self-reporting. Study limitations included a lack of data on nephrogenic rests, which may potentially modify the relationships we observed between fetal growth and Wilms tumor. Although statistical power was greater than in most previous studies, our ability to detect associations in certain exposure strata was still limited. Our findings warrant further confirmation in other large cohort studies including non-Nordic populations when feasible.

In summary, we found that high fetal growth was associated with increased risk of Wilms tumor with onset before age 5 years among girls born in Sweden during 1973-2008. These findings appear consistent with previous evidence for the role of perilobar nephrogenic rests and early-life growth factor pathways, which may be more common among girls than boys. Further investigation of these mechanisms is warranted and ultimately may reveal better targets for prevention or treatment of specific subtypes of Wilms tumor.

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Author Contributions: Dr. Jan Sundquist had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Crump, K. Sundquist, Sieh, Winkleby, J. Sundquist.

Acquisition of data: K. Sundquist, J. Sundquist.

Analysis and interpretation of data: Crump, K. Sundquist, Sieh, Winkleby, J. Sundquist.

Drafting of the manuscript: Crump.

Critical revision of the manuscript for important intellectual content: Crump, K. Sundquist, Sieh, Winkleby, J. Sundquist.

Statistical analysis: Crump, J. Sundquist.

Obtained funding: Crump, J. Sundquist.

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Table 1. Perinatal characteristics by Wilms tumor diagnosis (1973-2009)

	Girls		Boys	
	No Wilms (N=1,735,762) n (%)	**Wilms (N=224) n (%)**	**No Wilms (N=1,835,369) n (%)**	**Wilms (N=219) n (%)**
Birth year				
1973-1979	336,664 (19.4)	44 (19.6)	356,101 (19.4)	45 (20.6)
1980-1989	474,304 (27.3)	68 (30.4)	502,001 (27.3)	71 (32.4)
1990-1999	501,231 (28.9)	69 (30.8)	528,316 (28.8)	55 (25.1)
2000-2008	423,563 (24.4)	43 (19.2)	448,951(24.5)	48 (21.9)
Fetal growth (SD)				
<-1	295,360 (17.0)	36 (16.1)	292,578 (15.9)	31 (14.2)
-1 to <1	1,161,018 (66.9)	125 (55.8)	1,233,841 (67.2)	145 (66.2)
1 to <2	220,684 (12.7)	41 (18.3)	244,862 (13.3)	32 (14.6)
≥2	58,700 (3.4)	22 (9.8)	64,088 (3.5)	11 (5.0)
Birth weight (g)				
<2500	77,375 (4.5)	10 (4.5)	71,966 (3.9)	8 (3.7)
2500-3999	1,414,430 (81.5)	157 (70.1)	1,364,944 (74.4)	150 (68.5)
≥4000	243,957 (14.0)	57 (25.4)	398,459 (21.7)	61 (27.9)
Birth length (cm)				
<48	213,170 (12.3)	25 (11.2)	146,782 (8.0)	11 (5.0)
48-52	1,323,999 (76.3)	152 (67.9)	1,277,055 (69.6)	151 (69.0)
≥53	183,464 (10.6)	42 (18.8)	393,444 (21.4)	54 (24.7)
Unknown	15,129 (0.9)	5 (2.2)	18,088 (1.0)	3 (1.4)
Gestational age at birth (weeks)				
<37	94,628 (5.4)	17 (7.6)	112,185 (6.1)	14 (6.4)
37-41	1,503,188 (86.6)	190 (84.8)	1,562,726 (85.2)	186 (84.9)
≥42	137,946 (7.9)	17 (7.6)	160,458 (8.7)	19 (8.7)
Multiple birth				
Singleton	1,693,953 (97.6)	219 (97.8)	1,792,713 (97.7)	215 (98.2)
Twin or higher order	41,809 (2.4)	5 (2.2)	42,656 (2.3)	4 (1.8)
Birth order				
1	686,258 (39.5)	93 (41.5)	724,991 (39.5)	93 (42.5)
2	593,977 (34.2)	88 (39.3)	630,105 (34.3)	83 (37.9)
≥3	353,552 (20.4)	39 (17.4)	372,079 (20.3)	35 (16.0)
Unknown	101,975 (5.9)	4 (1.8)	108,194 (5.9)	8 (3.6)
Maternal age at delivery (years)				
<25	370,551 (21.4)	43 (19.2)	391,572 (21.3)	51 (23.3)
25-29	608,148 (35.0)	89 (39.7)	643,455 (35.1)	90 (41.1)
30-34	502,802 (29.0)	69 (30.8)	531,533 (29.0)	53 (24.2)
≥35	252,236 (14.5)	23 (10.3)	266,716 (14.5)	25 (11.4)
Unknown	2,025 (0.1)	0 (0.0)	2,093 (0.1)	0 (0.0)
Paternal age at delivery (years)				
<25	166,828 (9.6)	15 (6.7)	177,130 (9.7)	28 (12.8)
25-29	497,156 (28.6)	74 (33.0)	524,702 (28.6)	63 (28.8)
30-34	564,316 (32.5)	70 (31.3)	597,372 (32.6)	67 (30.6)
≥35	493,646 (28.4)	64 (28.6)	521,357 (28.4)	59 (26.9)
Unknown	13,816 (0.8)	1 (0.4)	14,808 (0.8)	2 (0.9)
Maternal education (years)				

≤9	328,629 (18.9)	35 (15.6)	346,494 (18.9)	41 (18.7)
10-11	559,618 (32.2)	71 (31.7)	590,616 (32.2)	76 (34.7)
12-14	507,974 (29.3)	75 (33.5)	537,376 (29.3)	64 (29.2)
≥15	268,798 (15.5)	37 (16.5)	286,025 (15.6)	35 (16.0)
Unknown	70,743 (4.1)	6 (2.7)	74,858 (4.1)	3 (1.4)
Paternal education (years)				
≤9	373,505 (21.5)	59 (26.3)	394,125 (21.5)	44 (20.1)
10-11	549,574 (31.7)	77 (34.4)	579,537 (31.6)	81 (37.0)
12-14	465,757 (26.8)	47 (21.0)	494,459 (26.9)	56 (25.6)
≥15	261,451 (15.1)	37 (16.5)	276,622 (15.1)	27 (12.3)
Unknown	85,475 (4.9)	4 (1.8)	90,626 (4.9)	11 (5.0)
Beckwith-Weidemann syndrome[a]	79 (<0.1)	6 (2.7)	106 (<0.1)	2 (0.9)
Family history of Wilms tumor[a]	407 (<0.1)	1 (0.4)	477 (<0.1)	2 (0.9)

[a]Ascertained through 2009.

Table 2. Adjusted hazard ratios for associations between perinatal characteristics and Wilms tumor (1973-2009)

	Girls			Boys		
	aHR[a]	95% CI	*P*	aHR[a]	95% CI	*P*
Birth year						
1973-1979	1.00			1.00		
1980-1989	1.07	0.73, 1.57	0.74	1.17	0.80, 1.72	0.41
1990-1999	1.02	0.69, 1.51	0.90	0.88	0.59, 1.33	0.55
2000-2008	1.04	0.66, 1.65	0.85	1.22	0.77, 1.92	0.39
Fetal growth (SD)						
<-1	1.14	0.78, 1.65	0.50	0.90	0.61, 1.32	0.58
-1 to <1	1.00			1.00		
1 to <2	1.77	1.24, 2.52	0.002	1.13	0.77, 1.67	0.52
≥2	3.65	2.31, 5.77	<0.001	1.53	0.83, 2.83	0.18
Per SD	1.36	1.20, 1.54	<0.001	1.10	0.97, 1.25	0.14
Birth weight (g)						
<2500	0.81	0.37, 1.75	0.59	0.96	0.41, 2.24	0.92
2500-3999	1.00			1.00		
≥4000	2.22	1.63, 3.02	<0.001	1.44	1.06, 1.96	0.02
Per 1000 g	1.95	1.49, 2.56	<0.001	1.26	0.96, 1.64	0.09
Birth length (cm)						
<48	0.92	0.58, 1.48	0.74	0.56	0.29, 1.11	0.10
48-52	1.00			1.00		
≥53	2.05	1.45, 2.90	<0.001	1.19	0.87, 1.63	0.28
Unknown	2.56	0.99, 6.61	0.05	1.36	0.41, 4.48	0.61
Per cm	1.14	1.07, 1.22	<0.001	1.05	0.98, 1.11	0.17
Gestational age at birth (weeks)						
<37	1.61	0.98, 2.65	0.06	1.14	0.66, 1.96	0.64
37-41	1.00			1.00		
≥42	0.98	0.59, 1.61	0.93	1.00	0.62, 1.60	0.99
Per week	0.98	0.91, 1.05	0.53	1.00	0.94, 1.08	0.90
Multiple birth						
Singleton	1.00			1.00		
Twin or higher order	0.93	0.37, 2.37	0.88	0.88	0.32, 2.45	0.81
Birth order						
1	1.00			1.00		
2	1.03	0.76, 1.40	0.85	1.05	0.77, 1.43	0.77
≥3	0.81	0.53, 1.22	0.31	0.81	0.53, 1.25	0.35
Unknown	0.77	0.28, 2.12	0.61	1.52	0.72, 3.20	0.28
Maternal age at delivery (years)						
<25	1.00			1.00		
25-29	1.19	0.81, 1.74	0.37	1.05	0.73, 1.50	0.80
30-34	1.13	0.74, 1.73	0.56	0.77	0.50, 1.18	0.23
≥35	0.78	0.45, 1.37	0.39	0.76	0.45, 1.30	0.32
Paternal age at delivery (years)						
<25	1.00			1.00		
25-29	1.53	0.85, 2.76	0.16	0.71	0.44, 1.16	0.17
30-34	1.32	0.70, 2.49	0.39	0.76	0.44, 1.29	0.30

≥35	1.68	0.86, 3.28	0.13	0.93	0.52, 1.67	0.82
Unknown	1.30	0.17, 9.91	0.80	1.42	0.33, 6.07	0.63
Maternal education (years)						
≤9	1.00			1.00		
10-11	1.12	0.75, 1.69	0.58	1.06	0.72, 1.55	0.78
12-14	1.42	0.94, 2.15	0.10	1.06	0.71, 1.59	0.77
≥15	1.45	0.89, 2.36	0.14	1.21	0.75, 1.96	0.44
Unknown	0.90	0.38, 2.14	0.81	0.37	0.12, 1.21	0.10
Paternal education (years)						
≤9	1.00			1.00		
10-11	0.82	0.58, 1.16	0.27	1.21	0.84, 1.76	0.31
12-14	0.58	0.38, 0.86	0.007	1.00	0.66, 1.51	0.99
≥15	0.75	0.47, 1.21	0.24	0.83	0.48, 1.41	0.49
Unknown	0.35	0.12, 0.96	0.04	1.39	0.71, 2.70	0.34

[a]Adjusted for age (as the Cox model time scale), fetal growth, gestational age at birth, birth order, maternal age, and maternal education level. Birth weight and birth length were examined in separate models as alternatives to the standardized fetal growth variable.
The reference category for all variables is indicated by HR 1.00.