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Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California

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Abstract

Purpose—We aimed to examine the influence of pre-pregnancy diabetes, pre-pregnancy body mass index (BMI), gestational diabetes, and gestational weight gain on childhood cancer risk in offspring.

Methods—We identified cancer cases (n=11,149) younger than age 6 years at diagnosis from the California Cancer Registry registered between 1988–2013. Controls (n=270,147) were randomly sampled from California birth records, and frequency-matched by year of birth to all childhood cancers during the study period. Exposure and covariate information was extracted from birth records. Unconditional logistic regression models were generated to assess the importance of pre-pregnancy diabetes, pre-pregnancy BMI, gestational diabetes, and gestational weight gain on childhood cancer risk.

Results—We observed increased risks of acute lymphoblastic leukemia (ALL) and Wilms' tumor in children of mothers with pre-pregnancy diabetes [odds ratio (OR) =1.37, 95% confidence interval (CI): (1.11, 1.69), OR=1.45, 95% CI: (0.97, 2.18), respectively]. When born to mothers who were overweight prior to pregnancy (BMI 25–<30), children were at increased risk of leukemia [OR=1.27, 95% CI: (1.01, 1.59)]. Insufficient gestational weight gain increased the risk of acute myeloid leukemia (AML) [OR=1.50 (95% CI: 0.92, 2.42)] while excessive gestational weight gain increased the risk of astrocytomas [OR=1.56, 95% CI: (0.97, 2.50)]. No associations were found between gestational diabetes and childhood cancer risk in offspring.

Conclusions—We estimated elevated risks of several childhood cancers in the offspring of mothers who had diabetes and were overweight prior to pregnancy, as well as mothers who gained insufficient or excessive weight. Since few studies have focused on these factors in relation to childhood cancer, replication of our findings in future studies is warranted.

Keywords

diabetes; gestational weight gain; BMI; childhood cancer epidemiology; risk factors

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Introduction

It is estimated that 10,380 new childhood cancer cases and 1,250 deaths will occur in the US alone in 2016 [1]. The incidence of pediatric cancer in the United States has increased at an annual rate of 0.6% between 1975 and 2010, most notably for ALL, AML, non-Hodgkin lymphoma, and testicular germ cell tumors. In large part, the factors contributing to these increasing trends are largely unknown, as few risk factors for childhood cancer have been established [2]. Known risk factors include ionizing radiation, prior chemotherapy, and congenital genetic syndromes such as Down syndrome, neurofibromatosis, Fanconi anemia, and Bloom Syndrome, though these are only suspected to contribute to 5% to 10% of childhood cancers [3].

Many studies have consistently reported higher birthweights with an increased risk of leukemia, particularly for ALL [4–6]. Several population-based studies have reported that increasing birthweight may also increase the risk of other childhood cancers, such as Wilms' tumor, central nervous system (CNS) tumors, soft tissue sarcomas, neuroblastomas, lymphomas, germ cell tumors, and malignant melanomas [6–8]. Non-linear relationships with birthweight have been noted for some cancer types, as hepatoblastoma has been shown to decrease in risk with increasing birthweight, and a U-shaped association has been observed for AML with birthweight [4, 5, 8].

Biological mechanisms potentially linking higher birthweight to childhood cancers are not yet fully understood, but it has been hypothesized that insulin-like growth factor-1 (IGF-1) may play a role since IGF-1 is positively associated with birthweight and has also been implicated in several forms of childhood cancer [9–11]. The IGFs stimulate cell proliferation, inhibit apoptosis, and are also important in blood cell formation and regulation since receptors for IGF-1 are found on cells of hematopoietic origin, and IGF-1 stimulates red blood cell production and regulates normal B-lymphocyte development [10, 12]. In the case of hepatoblastoma, which has consistently been related to low birthweight, it has been suggested that the relation may be explained by parental smoking or medical interventions in early life [13]. If myeloid cells are also particularly susceptible to these factors, this could explain the association between low birthweight and AML. Also IGF levels or particular gene variations and alterations that result in low birthweight may be selectively harmful for developing myeloid cells [14].

The impact of metabolic factors on childhood cancer risk has not been extensively studied and to date these studies have produced inconclusive results, with some suggestive evidence for a positive association between maternal diabetes and childhood leukemias and lymphomas, but inconsistent results for maternal BMI and gestational weight gain [6, 15–26]. We hypothesize that since maternal diabetes, obesity, and excess weight gain during pregnancy have been shown to promote fetal growth, these conditions will increase the risk of childhood cancers that have been associated with higher birthweight [27–31]. Whereas pre-pregnancy underweight and insufficient gestational weight gain, which have been linked to restricted fetal growth, will result in an increased risk of childhood cancers that have been associated with lower birthweight [27, 28, 32]. Given the increasing prevalence of obesity and overweight status among women of childbearing age and increasing rates of pre-

pregnancy and gestational diabetes deliveries in the US [33–35], we aim to assess the association between pre-pregnancy diabetes, gestational diabetes, pre-pregnancy BMI, and gestational weight gain on the risk of all childhood cancers before age 6 in a very large, diverse and population-based sample of children born in California, in which Hispanics are the dominant ethnicity.

Methods

Study population

This study includes children from the Air Pollution and Childhood Cancers (APCC) study previously described [36]. Childhood cancer cases aged 5 years or younger at diagnosis were identified from the California Cancer Registry from 1988–2013. This analysis was restricted to young children as we hypothesized that pregnancy exposures are likely to be more relevant to the etiology of cancers diagnosed in early childhood. Approximately 89% of cases were successfully matched to their birth certificate by first and last name, date of birth, and when available, social security number. It is likely that children we were unable to match were those who moved to California after birth but before the age of 6 years [37]. Controls were frequency-matched by year of birth to all childhood cancer cases during the study period (20:1 matching rate) and randomly selected from all California birth certificates. The rationale for choosing a 20:1 ratio was to ensure that in the APCC study, a study of environmental exposures, there would be sufficient controls selected who resided in rural areas. Selection criteria for controls consisted of absence of a cancer diagnosis before 6 years of age in California. Also, potential control children were excluded if they died of any cause prior to age 6 (n=1,792). We also excluded children that were missing sex (n=3), births that were likely not viable (gestational age <20 weeks and/or birthweight <500g) (n=169), and children diagnosed with Down syndrome (n=151). The latter was done because Down syndrome is a strong risk factor for childhood cancer [3] and potentially related to pregnancy-related characteristics, including maternal obesity [38]. Additionally, mothers who had extreme or implausible BMI values (<17 kg/m^2 or > 45 kg/m^2) and gestational weight gain values (< −2 kg or >32 kg) were excluded. Only cancer types with at least 5 exposed cases with respect to pre-pregnancy diabetes were considered for inclusion in our study. AML was also included since ALL and AML are thought to have distinct etiologies. The final sample included 11,149 cases and 270,147 controls. We examined the childhood cancer types classified according to their respective International Classification of Childhood Cancer, 3rd edition (ICCC-3) codes [39]: 5,034 leukemias (codes 011–015) of which 4,101 were ALL (code 011) and 706 were AML (code 012), 990 astrocytomas (code 032), 709 intracranial and intraspinal embryonal brain tumors (code 033), 445 germ cell tumors (code 101–105), 337 hepatoblastomas (code 071), 1,378 neuroblastomas (code 041), 741 retinoblastomas (code 050), 463 rhabdomyosarcomas (code 091), and 1,052 Wilms' tumors (code 061). Our study used de-identified records so we were not required to obtain informed consent. The institutional review boards of University of California Los Angeles and the Committee for the Protection of Human Subjects approved this study.

Study variables

California birth records were our source of covariate data, which among other factors include information on birthweight, child sex, parental age at child birth, parental race/ethnicity, parental education, method of payment for prenatal care (private insurance/Medi-Cal/self-pay, which we previously found to be related to family income [40]) and gestational age, based on date of last menses. Size for gestational age was defined as small if birthweight was less than the 10^{th} percentile and as large if it was greater than the 90^{th} percentile of the birthweight standards for a given gestational age, using the method of Alexander and colleagues [41]. The 10^{th} and 90^{th} percentile values were obtained for each gestational week (20–45 weeks) by maternal race/ethnicity (non-Hispanic white, Hispanic of any race, Black, Asian/Pacific Islander, and other) and child's sex based on the total singleton live births in California between 1988 and 2006. We also categorized birthweight as low (<2500 grams), normal (2500–3999 grams), and high (>4000 grams). Presence of pre-pregnancy and gestational diabetes (Yes/No) was ascertained using birth records, detailed information on blood glucose level or other diabetes markers was unavailable. Gestational diabetes was only collected on birth certificates starting in 2006. Pre-pregnancy BMI was derived using pre-pregnancy weight in kilograms divided by the square of height in meters, and was only collected on California birth certificates starting in 2007. Pre-pregnancy BMI was categorized according to the World Health Organization criteria: <18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal), 25–29.9 kg/m^2 (overweight), ≥30 kg/m^2 (obese) [42]. Gestational weight gain was defined as the difference in kilograms between maternal weight at delivery and pre-pregnancy weight, and was also recorded on birth certificates from 2007 onwards. Gestational weight gain was further categorized according to the Institute of Medicine (IOM) 2009 guidelines on optimal weight gain during pregnancy: 12.5–18 kg in underweight women (<18.5 kg/m^2), 11.5–16 kg in normal weight women (18.5–24.9 kg/m^2), 7–11.5 in overweight women (25–29.9 kg/m^2), and 5–9 kg in obese women (≥30 kg/m^2) [43]. Socioeconomic status was assessed with a census-based index that has been previously described [44] and combines seven census-level indicators: education, median household income, percent living 200% below the poverty level, percent blue-collar workers, percent older than 16 years in workforce without job, median rent, and median house value.

Statistical analysis

Unconditional logistic regression was used to examine the associations between pre-pregnancy diabetes, gestational diabetes, pre-pregnancy BMI, gestational weight gain, and childhood cancer types. We report crude and adjusted odds ratios (OR) and 95% confidence intervals (CI). Selection of covariates was based upon our own exploration of the data in terms of change-in-estimate-criteria (included covariates that changed estimates by 10% or more), the confounding structure explored in directed acyclic graphs (DAGs), as well as the literature [45–48]. The change-in-estimate criteria was used for each model and each cancer type. Covariates that met our change-in-estimate criteria for at least one cancer type were included in our final models. Our final adjusted models included the matching variable, year of birth, as well as maternal and paternal race/ethnicity, and maternal age (<20, 20–29, 30–34, 35+). Further adjustment for paternal age was considered, but after adjusting for maternal age it did not change effect estimates more than minimally. The socioeconomic

variables (parental education, method of payment for prenatal care, and census-based SES) and race/ethnicity using finer 4-level (White non-Hispanic/Hispanic of any race/Black/other) and 5-level race categorizations (White non-Hispanic/Hispanic of any race/Black/Asian/Pacific Islander/other) were considered for adjustment, but not included in final models as they impacted point estimates by <10%.

We conducted sensitivity analyses to assess the impact of missing values for pre-pregnancy BMI and gestational weight gain using multiple imputation methods (PROC MI and PROC MIANALYZE). Most point estimates and confidence intervals changed minimally (<10%) thus here we report results without imputations; we present multiple imputation results in Supplementary Table 3. We additionally tested the sensitivity of associations to the potential inter-relatedness of all exposure variables through mutual adjustment. We also examined the relation between gestational weight gain and gliomas using the Central Brain Tumor Registry of the United States (CBTRUS) definition of gliomas in order to compare our results to other studies [49]. Thus, these glioma cases overlap with astrocytoma cases. Finally, we investigated leukemia types other than AML and ALL in relation to pre-pregnancy BMI, and the effect of pre-pregnancy diabetes on leukemia stratified by birthweight group. Since our study was underpowered to examine all exposures for all cancer types, we relied on strength of the association and confidence interval width (whether it was almost entirely above or below the null) rather than on traditional statistical significance testing to identify exposures as either elevating or decreasing risk. All analyses were conducted using SAS 9.3 software (Cary, NC).

Results

Sociodemographic characteristics for cases and controls for the entire study period are shown in Table 1, along with their distribution for specific cancer types in Supplementary Table 1. We also report sociodemographic characteristics for cases and controls born 2006 and onwards in Supplementary Table 2 since many exposures were only collected after 2006. We observed a similar distribution of characteristics in both time periods. Cancer was more common among males than females (55% vs. 45%). Leukemia was the most common cancer type followed by CNS tumors. More than 40% of children had a Hispanic mother or father. A higher proportion of cases than controls had private payment for prenatal care. The distribution of parental age and census-based SES appeared similar between cases and controls, but differed more by specific cancer types.

Compared to controls, a higher proportion of ALL and Wilms' tumor cases had high birthweight whereas a higher proportion of germ cell tumor and hepatoblastoma cases had low birthweight. We also noted some differences in gestational age, with a higher proportion of ALL, germ cell, and Wilms' tumor cases born large for gestational age (LGA) and a higher proportion of small for gestational age (SGA) births for hepatoblastoma than controls. More preterm births occurred in AML, germ cell, and hepatoblastoma cases than controls. Birth Certificates had a higher proportion of data missing for pre-pregnancy BMI and gestational weight gain compared to all other variables (9–10%). Missing values did not differ by disease status for most of our variables except for intraspinal and intracranial

embryonal brain tumors, which had a much higher proportion of missing pre-pregnancy BMI and gestational weight gain values (Table 2).

Pre-pregnancy diabetes increased the risk of all leukemias combined and ALL [OR (95% CI): 1.23 (1.01, 1.49), 1.37 (1.11, 1.69), respectively]. We estimated an elevated risk to develop Wilms' tumor when mothers had a diagnosis of diabetes prior to pregnancy [OR (95% CI): 1.45 (0.97, 2.18)] (Table 3).

We observed an increased risk of all leukemias combined in unconditional logistic regression without [OR (95% CI): 1.27 (1.01, 1.59)] as well as with multiple imputations [OR (95% CI): 1.26 (1.01, 1.58) for those born to mothers with an overweight pre-pregnancy BMI, but the point estimates for ALL and AML were weaker and included the null value. We found that other leukemia subtypes (ICCC-3 codes 013–015) were strongly related to an overweight pre-pregnancy BMI in mothers [adjusted OR (95% CI): 2.18 (1.08, 4.41)] and largely responsible for the increased risk we saw with leukemia, however this result was based on a small sample size (42 cases). Also, an overweight pre-pregnancy BMI was associated with an increased risk of retinoblastoma [OR (95% CI): 1.40 (0.92, 2.14). In contrast an underweight pre-pregnancy BMI seemed to contribute to germ cell tumor risk [OR (95% CI): 2.14 (0.83, 5.51)]. Intracranial and intraspinal embryonal brain tumors showed a decreased risk with a BMI considered as being obese [OR (95% CI): 0.47 (0.22, 1.00)]. However, after multiple imputations to handle missing values, these associations between pre-pregnancy BMI and retinoblastoma, germ cell tumors, and intracranial and intraspinal embryonal brain tumors were attenuated (Table 3, Supplementary Table 3).

For gestational weight gain grouped according to the IOM 2009 guidelines, we observed a suggestive positive association between insufficient weight gain and AML [OR (95% CI): 1.50 (0.92, 2.43)]. We also found an elevated risk of astrocytoma with excessive gestational weight gain [OR (95% CI): 1.56 (0.97, 2.50)] (Table 3). When examining the effect of gestational weight gain on gliomas and low-grade gliomas (105 of our 165 gliomas were astrocytomas), we found a similarly elevated risk of gliomas with excessive gestational weight gain (insufficient weight gain: adjusted OR (95% CI): 1.32 (0.84 2.06), excessive weight gain: adjusted OR (95% CI): 1.37 (0.94, 2.00)), but no associations with low-grade gliomas (insufficient weight gain: adjusted OR (95% CI): 0.57 (0.24, 1.35), excessive weight gain: adjusted OR (95% CI): 0.67 (0.36, 1.30)). After multiple imputations, associations between gestational weight gain, and AML and astrocytoma were attenuated [OR (95% CI): 1.43 (0.86, 2.41), 1.49 (0.92, 2.43), respectively] (Supplementary Table 3).

In sensitivity analyses, when mutually adjusting for exposure variables, our estimates for the associations we found did not change or changed minimally (<10%) (data not shown). We also found that the effect of pre-pregnancy diabetes on leukemia risk was similar in those born in the range of normal and high birthweight, with a slightly larger point estimate for the high birthweight group (low birthweight: adjusted OR (95% CI): 0.63 (0.20, 1.98), normal birthweight: adjusted OR (95% CI): 1.20 (0.95, 1.51), high birthweight: adjusted OR (95% CI): 1.40 (0.92, 2.12).

Discussion

In this population-based study of California children, we found several positive associations between maternal conditions in the pre-gestational and gestational period, and risk of cancer in offspring. Most notably, we observed an increased risk of leukemia and Wilms' tumor in children of mothers with pre-pregnancy diabetes and an increased risk of leukemia in children of overweight mothers. In relation to gestational weight gain, we found an elevated risk of astrocytoma in children of mothers with excessive weight gain and of AML in children of mothers with inadequate weight gain.

The positive associations seen between pre-pregnancy diabetes and risk of leukemia, particularly ALL, have been reported in other population-based studies. These studies reported associations of similar magnitude between maternal diabetes and ALL (OR=1.44) and leukemia (OR=1.40)[17, 18], except for one study that failed to find any association (OR=1.00) [19]. However, these studies did not differentiate between pre-pregnancy and gestational diabetes. No studies to date have published on Wilms' tumor in relation to pre-pregnancy diabetes. Of the few studies that have specifically reported on gestational diabetes, several have found positive associations [ORs ranging from 2 to 3] with leukemia [18, 20, 21], and others have found no associations with hepatoblastoma and retinoblastoma [23, 24]. We found that several point estimates were elevated for gestational diabetes, but confidence intervals were too wide to draw conclusions from our results. This may be due to potential misclassification of gestational diabetes because women with pre-pregnancy diabetes who do not undergo early screening may be incorrectly diagnosed with gestational diabetes [50]. Thus, gestational diabetes comprises of a heterogeneous risk group of women with controlled diabetes and uncontrolled diabetes at the start of pregnancy. Consequently, though pre-pregnancy and gestational diabetes both result in maternal hyperglycemia, their impact on fetal development is dependent on the management of these conditions [51]. Maternal hyperglycemia increases fetal growth, alters fetal metabolism, and induces oxidative stress and epigenetic changes [28, 52, 53]. The pathways linking maternal diabetes to childhood cancer risk are not fully understood, but the associations we observed are likely explained by a combination of these factors, which may explain why we did not find a consistently higher risk for all childhood cancers that have been associated with accelerated fetal growth.

In children of overweight mothers, we found an increased risk of leukemia and retinoblastoma. In contrast, underweight appeared to increase the risk of germ cell tumors. The few studies that have assessed the relation between pre-pregnancy BMI and childhood cancer risk have produced conflicting and inconclusive results [6, 15, 16, 23–26]. Given the unexpected pattern of a greater risk of these cancers with overweight but a drop in risk with obesity, it is notable that two studies of leukemia and retinoblastoma also observed an attenuation of the size of the estimate in the obese group [24, 26]. This may be explained by an increased risk of competing outcomes that cause selective survival of affected fetuses specifically fetal death, stillbirth, and neonatal, perinatal, and infant deaths that have been consistently observed to be associated with higher BMI. A recent meta-analysis suggested a 2 to 3-fold increased risk of fetal loss with maternal obesity [54]. No studies have been published specifically on maternal BMI and germ cell tumors to our knowledge. In our study

we found that intracranial and intraspinal embryonal brain tumors seemed to show a decreased risk with obesity. In light of the mixed and limited findings in the literature between BMI and childhood cancers, it is possible that our findings with BMI are spurious in nature. However, it is plausible that maternal obesity could increase the risk of childhood cancers since it results in maternal hyperglycemia [28].

We found astrocytoma to be associated with excessive weight gain while inadequate weight gain was positively associated with AML. Most studies on gestational weight gain and childhood cancer have not defined pregnancy weight gain in terms of the IOM guidelines. The use of arbitrary weight gain cutoffs that fail to take pre-pregnancy BMI into account may not accurately reflect risk and are likely to have produced some of the inconsistent findings across studies [15, 18, 19, 23, 25, 26]. A study that used the IOM 2009 guidelines found that both inadequate and excessive weight gain were associated with an increased risk of childhood brain tumors and low-grade gliomas [16]. We found an elevated risk of overall gliomas with excessive gestational weight gain, but none with low-grade gliomas. Birth certificates do not collect information on trimester-specific weight gain, which may be relevant since studies have shown that birthweight is dependent on the timing of weight gain during pregnancy [55]. This may explain why our observations were only partially explained by our hypotheses.

This study has several limitations. The use of birth certificate data avoids recall bias in this study since exposure information is ascertained prior to disease status, however the possibility of exposure misclassification bias exists. Validity of birthweight, race/ethnicity, and other demographic characteristics reported on birth certificate is typically high [56], while pre-pregnancy diabetes and gestational diabetes typically have low sensitivity and high specificity [57]. Thus, nondifferential underreporting of pre-pregnancy diabetes and gestational diabetes is likely and would have biased our estimates towards the null.

The validity of birth certificate-derived pre-pregnancy BMI and gestational weight gain is also of concern. In a Florida study, pre-pregnancy BMI based on weight and height reported on the birth certificate was shown to have an overall high specificity of 97% for underweight, 82% for normal weight, 88% for overweight, and 98% for obesity. Sensitivity was generally lower with a sensitivity of 77% for underweight, 86% for normal weight, 61% for overweight, and 76% for obesity [58]. A Pennsylvania study showed that agreement between pregnancy weight gain on birth records and medical records tends to be poorest for very low and very high weight gain. Errors in pre-pregnancy weight seem to be the main source of misclassification of pre-pregnancy BMI and gestational weight gain, which is plausible since pre-pregnancy weight recorded on the birth certificate is typically ascertained by maternal recall at delivery [59]. Although our multiple imputation analyses for missing values for pre-pregnancy BMI and gestational weight gain changed results minimally, this method relies on the assumption that the data are missing at random.

Another limitation of our study was our small sample size for gestational diabetes, pre-pregnancy BMI, and gestational weight gain since this information was only provided on birth certificates for a few years. Thus, our analyses were underpowered. As with all records-based studies, we lacked detailed information on our exposures of interest such as

type, duration, and treatment of maternal diabetes. We also lacked information on cytogenetic characteristics of cancer types, so we were unable to explore differential risk for cytogenetic abnormalities. Since our study sample only included children under 6 years of age, the generalizability of our findings to cancers in older children is limited. Lastly, it is possible that some of our findings could be explained by chance, particularly for those without prior supporting evidence in the literature, due to the many associations we examined and the multiple comparisons we did not adjust for.

Strengths of the study include the prospective population-based design and the inclusion of various childhood cancer types. It is one of few studies to date that focused on assessing the impact of maternal weight and diabetes in pregnancy on childhood cancer risk, which is highly relevant for the US population given the current epidemic of obesity and its link with diabetes. This is particularly important in this predominantly Hispanic population as Hispanics in California have one of the highest incidence rates of childhood cancer worldwide [60]. Few studies have differentiated between pre-pregnancy and gestational diabetes and assessed weight gain according to IOM 2009 guidelines. We hope that this study underscores the importance of drawing these distinctions so that results across studies can be readily compared.

In conclusion, in our sample of California children, pre-pregnancy diabetes in mothers increased the risk of leukemia and particularly ALL in California children, and we estimated elevated risks for several childhood cancers in relation to pre-pregnancy BMI and gestational weight gain. Our study supports a potential role for these maternal conditions in affecting childhood cancer risk in offspring. These factors should be further investigated by pooling data in order to increase statistical power for these rare childhood cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Sociodemographic characteristics of cases and controls, birth years 1988–2011

	Controls (n=270147) n (%)	Cases (n=11149) n (%)
Child sex		
Male	137903 (51.1)	6135 (55.0)
Female	132244 (49.0)	5014 (45.0)
Maternal age at birth		
<20	28520 (10.6)	1083 (9.7)
20–29	140146 (51.9)	5577 (50.0)
30–34	62952 (23.3)	2743 (24.6)
35+	38479 (14.2)	1744 (15.6)
Missing	50 (0.02)	2 (0.02)
Father's age		
<20	10331 (3.8)	358 (3.2)
20–29	111645 (41.3)	4491 (40.3)
30–34	64765 (24.0)	2793 (25.1)
35+	65683 (24.3)	2927 (26.3)
Missing	17723 (6.6)	580 (5.2)
Mother race/ethnicity		
White non-Hispanic	94660 (35.0)	4364 (39.1)
Hispanic of any race	123975 (45.9)	4938 (44.3)
Other/not specified	51512 (19.1)	1847 (16.6)
Father's race/ethnicity		
White non-Hispanic	83101 (30.8)	3978 (35.7)
Hispanic of any race	117684 (43.6)	4687 (42.0)
Other/not specified	69362 (25.7)	2484 (22.3)
Maternal Education[a]		
8 or less years	29283 (12.4)	1098 (11.3)
9–11 years	42758 (18.1)	1613 (16.6)
12 years	65640 (27.8)	2834 (29.1)
13 to 15 years	47105 (19.9)	1920 (19.7)
16 or more years	47137 (20.0)	2093 (21.5)
Missing	4411 (1.9)	169 (1.7)
Paternal Education[a]		
8 or less years	29845 (12.6)	1123 (11.6)
9–11 years	33292 (14.1)	1267 (13.0)
12 years	65536 (27.7)	2767 (28.5)
13 to 15 years	39220 (16.6)	1684 (17.3)
16 or more years	48540 (20.5)	2184 (22.5)

	Controls (n=270147) n (%)	Cases (n=11149) n (%)
Missing	19901 (8.4)	702 (7.2)
Source of payment for prenatal care[a]		
Private	116717 (49.4)	5332 (54.8)
Medi-Cal/other governmental/self-pay	116935 (49.5)	4323 (44.4)
Missing	2682 (1.1)	72 (0.7)
Census-based SES		
1 (lowest)	67375 (24.9)	2571 (23.1)
2	65424 (24.2)	2741 (24.6)
3	59729 (22.1)	2495 (22.4)
4	42568 (15.8)	1806 (16.2)
5 (highest)	34279 (12.7)	1520 (13.6)
Missing	772 (0.3)	16 (0.1)

[a]Collected starting 1989

Table 2

Maternal and perinatal characteristics of cases and controls, birth years 1988–2011

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytomas n (%)	Intracranial and intraspinal embryonal tumors n (%)	Germ cell tumors n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms' tumor n (%)
n	270147	5034	4101	706	990	709	445	337	1378	741	463	1052
Birthweight												
<2500 g	15932 (5.9)	246 (4.9)	183 (4.5)	48 (6.8)	55 (5.6)	55 (7.8)	40 (9.0)	79 (23.4)	91 (6.6)	50 (6.8)	28 (6.1)	56 (5.3)
2500–3999 g	226158 (83.7)	4160 (82.6)	3390 (82.7)	587 (83.1)	818 (82.6)	575 (81.1)	356 (80.0)	230 (68.3)	1124 (81.6)	616 (83.1)	380 (82.1)	832 (79.1)
4000+ g	27824 (10.3)	625 (12.4)	526 (12.8)	70 (9.9)	116 (11.7)	79 (11.1)	49 (11.0)	28 (8.3)	160 (11.6)	75 (10.1)	55 (11.9)	159 (15.1)
Missing	233 (0.1)	3 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	5 (0.5)
Size for gestational age												
Small for gestational age	27258 (10.1)	429 (8.5)	327 (8.0)	77 (10.9)	92 (9.3)	63 (8.9)	34 (7.6)	54 (16.0)	129 (9.4)	76 (10.3)	50 (10.8)	90 (8.6)
Normal for gestational age	204806 (75.8)	3787 (75.2)	3095 (75.5)	532 (75.4)	749 (75.7)	541 (76.3)	326 (73.3)	237 (70.3)	1047 (76.0)	566 (76.4)	344 (74.3)	766 (72.8)
Large for gestational age	37850 (14.0)	815 (16.2)	677 (16.5)	96 (13.6)	148 (15.0)	105 (14.8)	85 (19.1)	46 (13.7)	199 (14.4)	99 (13.4)	69 (14.9)	191 (18.2)
Missing	233 (0.1)	3 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	5 (0.5)
Gestational age												
37 or less weeks (Preterm)	26226 (9.7)	532 (10.6)	404 (9.9)	104 (14.7)	96 (9.7)	82 (11.6)	85 (19.1)	80 (23.7)	149 (10.8)	75 (10.1)	40 (8.6)	120 (11.4)
38–42 weeks (Term)	221370 (81.9)	4067 (80.8)	3333 (81.3)	548 (77.6)	817 (82.5)	560 (79.0)	320 (71.9)	236 (70.0)	1113 (80.8)	614 (82.9)	381 (82.3)	857 (81.5)
43 or more weeks (Post	9810 (3.6)	190 (3.8)	159 (3.9)	24 (3.4)	30 (3.0)	28 (4.0)	17 (3.8)	7 (2.1)	61 (4.4)	25 (3.4)	20 (4.3)	30 (2.9)

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytomas n (%)	Intracranial and intraspinal embryonal tumors n (%)	Germ cell tumors n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms' tumor n (%)
term)												
Missing	12741 (4.7)	245 (4.9)	205 (5.0)	30 (4.3)	47 (4.8)	39 (5.5)	23 (5.2)	14 (4.2)	55 (4.0)	27 (3.6)	22 (4.8)	45 (4.3)
Pre-pregnancy diabetes												
Yes	4289 (1.6)	104 (2.1)	94 (2.3)	4 (0.6)	11 (1.1)	6 (0.9)	7 (1.6)	7 (2.1)	18 (1.3)	11 (1.5)	5 (1.1)	25 (2.4)
No	265858 (98.4)	4930 (97.9)	4007 (97.7)	702 (99.4)	979 (98.9)	703 (99.2)	438 (98.4)	330 (97.9)	1360 (98.7)	730 (98.5)	458 (98.9)	1027 (97.6)
Gestational diabetes[a]												
Yes	1667 (3.2)	24 (3.7)	17 (4.0)	4 (2.4)	6 (4.1)	5 (4.0)	2 (2.2)	5 (5.3)	12 (4.1)	7 (4.4)	1 (1.2)	7 (3.6)
No	50133 (96.8)	628 (96.3)	412 (96.0)	163 (97.6)	141 (95.9)	119 (96.0)	88 (97.8)	89 (94.7)	282 (95.9)	152 (95.6)	84 (98.8)	186 (96.4)
Mother's height (m)[b]												
<1.57 m	8350 (21.2)	96 (21.5)	49 (18.1)	30 (23.4)	17 (15.0)	18 (20.2)	16 (22.5)	22 (28.6)	45 (19.1)	20 (16.3)	9 (15.8)	25 (17.1)
1.57–<1.65 m	16000 (40.6)	177 (39.7)	120 (44.3)	45 (35.2)	38 (33.6)	39 (43.8)	27 (38.0)	32 (41.6)	73 (30.9)	47 (38.2)	21 (36.8)	53 (36.3)
≥1.65 m	13136 (33.3)	155 (34.8)	92 (34.0)	46 (35.9)	56 (49.6)	24 (27.0)	26 (36.6)	23 (29.9)	102 (43.2)	48 (39.0)	26 (45.6)	62 (42.5)
Missing	1973 (5.0)	18 (4.0)	10 (3.7)	7 (5.5)	2 (1.8)	8 (9.0)	2 (2.8)	0 (0.0)	16 (6.8)	8 (6.5)	1 (1.8)	6 (4.1)
Pre-pregnancy weight (kg)[b]												
<56 kg	8945 (22.7)	94 (21.1)	54 (19.9)	31 (24.2)	18 (15.9)	24 (27.0)	17 (23.9)	25 (32.5)	47 (19.9)	25 (20.3)	12 (21.1)	24 (16.4)
56–<68 kg	13148 (33.3)	139 (31.2)	89 (32.8)	39 (30.5)	37 (32.7)	31 (34.8)	25 (35.2)	22 (28.6)	85 (36.0)	38 (30.9)	16 (28.1)	64 (43.8)
68–<80 kg	8108 (20.6)	105 (23.5)	58 (21.4)	30 (23.4)	30 (26.6)	18 (20.2)	15 (21.1)	12 (15.6)	44 (18.6)	37 (30.1)	13 (22.8)	24 (16.4)

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytomas n (%)	Intracranial and intraspinal embryonal tumors n (%)	Germ cell tumors n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms' tumor n (%)
≥80 kg	6167 (15.6)	73 (16.4)	48 (17.7)	19 (14.8)	22 (19.5)	5 (5.6)	8 (11.3)	12 (15.6)	44 (18.6)	15 (12.2)	12 (21.1)	24 (16.4)
Missing	3091 (7.8)	35 (7.9)	22 (8.1)	9 (7.0)	6 (5.3)	11 (12.4)	6 (8.5)	6 (7.8)	16 (6.8)	8 (6.5)	4 (7.0)	10 (6.9)
Pre-pregnancy BMI[b]												
<18.5	1249 (3.2)	8 (1.8)	5 (1.9)	3 (2.3)	4 (3.5)	4 (4.5)	5 (7.0)	3 (3.9)	7 (3.0)	2 (1.6)	2 (3.5)	1 (0.7)
18.5–<25	18484 (46.8)	195 (43.7)	123 (45.4)	57 (44.5)	51 (45.1)	44 (49.4)	34 (47.9)	38 (49.4)	112 (47.5)	52 (42.3)	27 (47.4)	78 (53.4)
25–<30	9352 (23.7)	125 (28.0)	74 (27.3)	34 (26.6)	30 (26.6)	21 (23.6)	16 (22.5)	14 (18.2)	55 (23.3)	40 (32.5)	13 (22.8)	33 (22.6)
30+	6758 (17.1)	80 (17.9)	47 (17.3)	23 (18.0)	20 (17.7)	8 (9.0)	10 (14.1)	16 (20.8)	43 (18.2)	19 (15.5)	11 (19.3)	22 (15.1)
Missing	3616 (9.2)	38 (8.5)	22 (8.1)	11 (8.6)	8 (7.1)	12 (13.5)	6 (8.5)	6 (7.8)	19 (8.1)	10 (8.1)	4 (7.0)	12 (8.2)
Gestational weight gain (kg)[b]												
<0	161 (0.4)	1 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.4)	1 (0.8)	0 (0.0)	1 (0.7)
0–<10	9801 (24.8)	126 (28.3)	70 (25.8)	38 (29.7)	24 (21.2)	27 (30.3)	19 (26.8)	16 (20.8)	51 (21.6)	27 (22.0)	11 (19.3)	39 (26.7)
10–<15	12183 (30.9)	125 (28.0)	74 (27.3)	36 (28.1)	32 (28.3)	23 (25.8)	21 (29.6)	24 (31.2)	80 (33.9)	46 (37.4)	17 (29.8)	47 (32.2)
15–<20	8601 (21.8)	93 (20.9)	59 (21.8)	28 (21.9)	34 (30.1)	19 (21.4)	15 (21.1)	20 (26.0)	49 (20.8)	27 (22.0)	14 (24.6)	32 (21.9)
≥20	5022 (12.7)	60 (13.5)	42 (15.5)	15 (11.7)	17 (15.0)	8 (9.0)	9 (12.7)	10 (13.0)	35 (14.8)	13 (10.6)	11 (19.3)	17 (11.6)
Missing	3691 (9.4)	41 (9.2)	26 (9.6)	10 (7.8)	6 (5.3)	12 (13.5)	6 (8.5)	7 (9.1)	20 (8.5)	9 (7.3)	4 (7.0)	10 (6.9)

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytomas n (%)	Intracranial and intraspinal embryonal tumors n (%)	Germ cell tumors n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms' tumor n (%)
Gestational weight gain (IOM 2009 guidelines)[b]												
Not enough weight	8089 (20.5)	94 (21.1)	50 (18.5)	35 (27.3)	22 (19.5)	21 (23.6)	18 (25.4)	13 (16.9)	39 (16.5)	22 (17.9)	10 (17.5)	31 (21.2)
IOM recommended	10698 (27.1)	132 (29.6)	83 (30.6)	31 (24.2)	24 (21.2)	27 (30.3)	18 (25.4)	20 (26.0)	68 (28.8)	33 (26.8)	16 (28.1)	45 (30.8)
Too much	16550 (41.9)	177 (39.7)	112 (41.3)	50 (39.1)	59 (52.2)	28 (31.5)	29 (40.9)	37 (48.1)	106 (44.9)	57 (46.3)	27 (47.4)	58 (39.7)
Missing	4122 (10.5)	43 (9.6)	26 (9.6)	12 (9.4)	8 (7.1)	13 (14.6)	6 (8.5)	7 (9.1)	23 (9.8)	11 (8.9)	4 (7.0)	12 (8.2)

[a] Collected starting 2006

[b] Collected starting 2007

Table 3

Odds ratios and 95% CIs from logistic regression models for childhood cancers in relation to pre-pregnancy diabetes, gestational diabetes, pre-pregnancy BMI, and gestational weight gain

	Leukemia		ALL		AML		Astrocytomas		Intracranial & intraspinal embryonal brain tumors		Germ cell tumors		Hepatoblastoma		Neuroblastoma		Retinoblastoma		Rhabdomyosarcoma		Wilms' tumor	
	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]
Birth years 1983–2011																						
Pre-pregnancy diabetes																						
Yes	1.31	1.23 (1.01, 1.49)	1.46	1.37 (1.11, 1.69)	0.36	---	0.70	0.71 (0.39, 1.30)	0.53	0.54 (0.24, 1.20)	0.99	0.97 (0.46, 2.06)	1.34	1.22 (0.58, 2.60)	0.82	0.85 (0.53, 1.35)	0.94	0.93 (0.51, 1.69)	0.68	0.66 (0.27, 1.60)	1.51	1.45 (0.97, 2.18)
Birth years 2006–2011																						
Gestational diabetes																						
Yes	1.17	1.14 (0.76, 1.72)	1.29	1.26 (0.77, 2.05)	0.74	---	1.29	1.32 (0.58, 3.02)	1.27	1.25 (0.51, 3.07)	0.68	---	1.65	1.49 (0.60, 3.70)	1.26	1.31 (0.73, 2.34)	1.36	1.34 (0.63, 2.88)	0.37	---	1.14	1.23 (0.57, 2.63)
Birth years 2007–2011																						
Pre-pregnancy BMI																						
<18.5	0.61	0.62 (0.31, 1.27)	0.60	0.62 (0.25, 1.52)	0.78	---	1.16	---	1.35	---	2.18	2.14 (0.83, 5.51)	1.17	---	0.93	0.90 (0.42, 1.94)	0.57	---	1.09	---	0.19	---
18.5–<25	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25–<30	1.28	1.27 (1.01, 1.59)	1.21	1.17 (0.88, 1.57)	1.18	1.22 (0.80, 1.88)	1.17	1.28 (0.81, 2.03)	0.94	0.91 (0.54, 1.53)	0.92	0.94 (0.52, 1.72)	0.72	0.71 (0.38, 1.31)	0.97	1.05 (0.76, 1.45)	1.51	1.40 (0.92, 2.14)	0.96	0.96 (0.49, 1.88)	0.84	0.85 (0.56, 1.28)
30+	1.14	1.13 (0.86, 1.47)	1.08	1.03 (0.73, 1.45)	1.10	1.17 (0.71, 1.91)	1.08	1.23 (0.73, 2.09)	0.50	0.47 (0.22, 1.00)	0.80	0.82 (0.40, 1.68)	1.13	1.10 (0.60, 1.99)	1.04	1.16 (0.81, 1.66)	0.98	0.88 (0.52, 1.51)	1.13	1.13 (0.55, 2.30)	0.78	0.79 (0.49, 1.28)
Gestational weight gain (IOM 2009 guidelines)																						
Not enough weight	0.93	0.93 (0.71, 1.21)	0.78	0.78 (0.55, 1.11)	1.50	1.50 (0.92, 2.43)	1.20	1.28 (0.72, 2.28)	1.03	1.05 (0.59, 1.86)	1.33	1.31 (0.68, 2.52)	0.87	0.85 (0.42, 1.72)	0.76	0.80 (0.54, 1.19)	0.89	0.88 (0.51, 1.52)	0.82	0.85 (0.38, 1.87)	0.91	0.93 (0.59, 1.47)
IOM recommended	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

	Leukemia		ALL		AML		Astrocytomas		Intracranial & intraspinal embryonal brain tumors		Germ cell tumors		Hepatoblastoma		Neuroblastoma		Retinoblastoma		Rhabdomyosarcoma		Wilms' tumor	
	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]	Crude OR[a]	OR (95% CI)[b, c]
Too much	0.86	0.86 (0.69, 1.08)	0.66	0.86 (0.65, 1.14)	1.04	1.05 (0.67, 1.64)	1.58	1.56 (0.97, 2.50)	0.67	0.66 (0.39, 1.13)	1.05	1.07 (0.59, 1.94)	1.20	1.25 (0.72, 2.16)	1.01	1.00 (0.74, 1.36)	1.12	1.15 (0.74, 1.76)	1.08	1.06 (0.57, 1.97)	0.83	0.80 (0.54, 1.19)

[a] Adjusted for the matching variable, year of birth

[b] Adjusted for year of birth, maternal/paternal race/ethnicity, maternal age

[c] Adjusted OR estimates were not calculated for categories with <5 exposed cases