Title

Prenatal risk factors for childhood cancer and placental vascular resistance: an investigation of maternal metabolic factors and smoking, Hispanic enclaves, and air pollution

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Publication Date

2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Prenatal risk factors for childhood cancer and placental vascular resistance: an investigation of maternal metabolic factors and smoking, Hispanic enclaves, and air pollution

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Zuelma Arellano Contreras

2017

ABSTRACT OF THE DISSERTATION

Prenatal risk factors for childhood cancer and placental vascular resistance: an investigation of maternal metabolic factors and smoking, Hispanic enclaves, and air pollution

by

Zuelma Arellano Contreras

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2017

Professor Beate R. Ritz, Chair

It is hypothesized that about half of all childhood cancers have prenatal origins. The first two studies of this dissertation focus on prenatal risk factors for childhood cancers. The first study includes cancer cases identified from the California Cancer Registry and diagnosed under six years of age between 1988 and 2013. Controls were selected from California birth records and matched to cases on birth year. Using birth certificate information, we assessed the association between pre-pregnancy diabetes, gestational diabetes, pre-pregnancy body mass index, gestational weight gain, and childhood cancer risk. We found an increased risk of acute lymphoblastic leukemia in offspring of mothers with pre-pregnancy diabetes.

Our second study includes the same sample of children, but limited to children of Hispanic mothers. Census tract data from the US decennial census (1990, 2000) and the American Community Survey (2007-2011) was used to create an index measure of Hispanic enclaves. Overall, offspring of mothers residing outside of Hispanic enclaves during pregnancy were at reduced risk of acute myeloid leukemia, hepatoblastoma, and retinoblastoma.

The effect of prenatal exposures can also be assessed using measures of placental vascular resistance, which have been shown to be predictive of adverse pregnancy outcomes. In the third study, we examined whether prenatal exposure to air pollution and smoking increases placental vascular resistance. Our sample includes pregnant women recruited between 1993 and 1996 in Los Angeles, California. We found that air pollution exposure increased uterine artery resistance in late pregnancy. Additionally, being a former smoker increases umbilical resistance in late pregnancy while smoking during pregnancy increases umbilical resistance, and uterine resistance and notching in mid-pregnancy.

In conclusion, our findings underline the importance of management of diabetes during pregnancy in childhood cancer prevention. Our results also suggest that Hispanic women living in densely populated Hispanic neighborhoods may be more vulnerable to certain risk factors as offspring of mothers living outside of these enclaves had a reduced risk of some cancers. Lastly, our results for prenatal air pollution and smoking support that both influence placental vascular resistance, providing insight on a potential mechanistic link between these exposures and adverse pregnancy outcomes.

The dissertation of Zuelma Arellano Contreras is approved.

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LIST OF ABBREVIATIONS

Acute lymphoblastic leukemia (ALL)

Acute myeloid leukemia (AML)

Air Pollution and Childhood Cancers (APCC)

American Community Survey (ACS)

BMI (body mass index)

Carbon monoxide (CO)

Central Brain Tumor Registry of the United States (CBTRUS)

Central nervous system (CNS)

Confidence interval (CI)

Developmental Origins of Health and Disease (DoHAD)

Directed acyclic graph (DAG)

Geographic information systems (GIS)

Gestational weight gain (GWG)

Institute of Medicine (IOM)

Insulin-like growth factor (IGF)

International Classification of Childhood Cancer (ICCC)

International Classification of Diseases for Oncology (ICD-O)

Intrauterine growth restriction (IUGR)

Large for gestational age (LGA)

Nitrogen dioxide (NO_2)

Non-Hodgkin lymphoma (NHL)

Odds ratio (OR)

Ozone (O_3)

Particulate matter (PM)

Rural-urban commuting area (RUCA)

Small for gestational age (SGA)

Socioeconomic status (SES)

Standard deviation (SD)

World Health Organization (WHO)

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Beate Ritz, for her constant guidance and support throughout this program. She taught me many valuable lessons inside and outside of the classroom. I deeply admire her notable contributions to the field of epidemiology and her passion for striving to conduct impactful and quality research. I am very grateful to have had her as my mentor and will remember her teachings as I embark upon my career in epidemiology. I would also like to thank my informal advisor, Dr. Julia Heck, who spent countless hours reading my work and providing me with guidance through every step of the program. She gave me the opportunity to collaborate with her on various projects as her Graduate Student Researcher and gain valuable experience in the field. Her dedication to her students and to her research is evident and I consider myself lucky to have had her as my mentor.

I would also like to express my gratitude to my committee members. Dr. Onyebuchi Arah, who helped me understand the complexities of epidemiologic research and to challenge myself long before he was on my committee. Dr. Ondine von Ehrenstein who was always available for routine discussions and for the extensive insight she provided at the intersection of epidemiology and community health science. Dr. Anne Pebley, who shared her valuable expertise in neighborhood health research and encouraged and supported me immensely.

I would also like to thank my fellow classmates at UCLA who helped lift me up through the ups and downs of the program. I am also deeply grateful for the financial support I received from the UCLA Department of Epidemiology, the Graduate Division, and Tobacco-Related Disease Research Program which allowed me to focus on my studies and finish in a timely manner. I would also like to give special thanks to Dr. Zuo-Feng Zhang who provided me with

the opportunity to be on the UCLA Molecular Genetic Epidemiology of Cancer Training Program.

My deepest appreciation goes to my family, to whom I dedicate this work to. They instilled in me the passion and dedication for public health that pushed me to where I am today. Last, but not least, I would like to thank my husband who began this journey with me many years ago and provided me with endless support, love, and encouragement.

Chapter 1 is incorporated from Contreras ZA, Ritz B, Virk J, Cockburn M, Heck JE. 2016. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control 27(10):1273-1285. doi: 10.1007/s10552-016-0807-5. ©Springer, with kind permission from Springer. Beate Ritz and Julia E Heck assisted in the project design and manuscript editing. Myles Cockburn provided the data and assisted in manuscript editing. Jasveer Virk assisted in manuscript editing.

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Heck JE, **Contreras ZA**, Park AS, Davidson TB, Cockburn M, Ritz B. Smoking in pregnancy and risk of cancer among young children: a population-based study. 2016. Int J Cancer 139(3):613-616. doi: 10.1002/ijc.30111.

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Chapter 1. Introduction and background

1.1 The prenatal environment

The importance of the prenatal environment has long been recognized since the work of David Barker and colleagues in the mid-1980s in which they found associations between low birthweight and increased risk of coronary heart disease, stroke, hypertension, and type 2 diabetes in later life. The developmental origins of health and disease (DOHaD) hypothesis, developed from this work, proposes that adaptations made by the fetus to the intra-uterine environment result in permanent changes that affect long-term health and susceptibility to disease [1–3]. Early studies hypothesized that undernutrition during early life was largely responsible for the programming of these long-term health outcomes [1]. However, since then studies have expanded the concept of fetal programming to consider the potential impacts of perturbations anywhere along the entire fetal-supply line, including uteroplacental blood flow, placental function, and fetal metabolism [4]. This dissertation aims to examine a number of individual and environmental level factors, acting either independently or synergistically in the prenatal period, and their impact on perinatal and childhood health outcomes. Briefly, the first two studies of this dissertation assess cancer risk in a population-based sample of California children in relation to maternal diabetes, obesity, and gestational weight gain (GWG), and residence in a densely populated Hispanic neighborhood during pregnancy. The third study examines the potential effects of prenatal exposure to air pollution and smoking in relation to placental vascular resistance in a sample of pregnant women living in Los Angeles, California.

1.2 Offspring health outcomes

1.2.1 Childhood cancers

Approximately 10,380 new cancer cases and 1,250 deaths will occur among children under 14 years of age in the US in 2016. Leukemia accounts for the majority of childhood cancers (30%), followed by brain and other central nervous system (CNS) tumors (26%), soft tissue sarcomas (7%), neuroblastoma (6%), non-Hodgkin lymphomas (NHL) (6%), Wilms' tumors (5%), and Hodgkin lymphomas (3%). Cancer is the second leading cause of pediatric death after accidents. Despite a slight increase in the incidence of cancers in children and adolescents of 0.6% per year from 1975-2012, the cancer death rate declined by 65% in children from 1970 to 2012 [5].

In California, the most common pediatric cancer types are similar to those seen nationally with leukemia (31%) and brain and other CNS tumors (25%) accounting for the most cases. Compared to the US, the cancer incidence rate between 2008-2012 was the same for non-Hispanic whites, 4% higher among African Americans, 3% higher among Hispanics, and 13% higher among Asian/Pacific Islanders. In 2013, the age-adjusted rate of childhood cancers was highest in non-Hispanic whites (19.7 per 100,000) followed by Hispanics (15.3 per 100,000), non-Hispanic Blacks (14.4 per 100,000), and Asian/Pacific Islander (13.6 per 100,000) [6]. However, rates vary by cancer type with studies finding higher rates of acute lymphoblastic leukemia (ALL) in Hispanics and lower rates of brain and CNS tumors compared to non-Hispanic whites [7, 8].

Mortality rates for childhood cancer in California have declined by 64% from 1973-2013. The 5-year survival rate for diagnoses between 2004-2013 for all cancers combined was about

82%. Dramatic improvements in treatment for leukemia have led to brain cancer replacing leukemia as the most common cause of cancer death among children (<19 years) in 2012 [5]. Late treatment-related side effects of pediatric cancer include impairment in the function of certain organs, secondary cancers, and cognitive deficits [6].

There are few well-established risk factors for childhood cancers. High-dose ionizing radiation and prior chemotherapy are accepted causes of childhood cancers [9]. Higher birthweight has been shown to be consistently associated with an increased risk of ALL, CNS tumors, neuroblastoma, and Wilms tumor, whereas lower birthweight has been associated with an increased risk of hepatoblastoma. A U-shaped association has been observed for acute myeloid leukemia (AML). Older maternal age has been positively associated with most caner types (leukemia, lymphoma, CNS tumors, neuroblastoma, Wilms' tumor, bone tumors, and soft tissue sarcomas), however the evidence for older paternal age is less consistent with strong evidence existing only for ALL [10–12]. Structural birth defects and congenital genetic syndromes such as Down syndrome, neurofibromatosis, Fanconi anemia, and Bloom syndrome have been shown to increase the risk of some childhood cancers [13, 14].

1.2.2 Placental vascular resistance

The placenta receives blood from both the maternal and fetal systems: the maternal-placental (uteroplacental) blood circulation and the fetal-placental (fetoplacental) blood circulation. The uteroplacental blood circulation is responsible for the delivery of oxygen and nutrients to the fetus whereas the fetoplacental blood circulation carries deoxygenated and nutrient-depleted fetal blood from the fetus [15]. Doppler ultrasound has long been used to assess placental resistance to blood flow and to register the presence of 'notching' in uterine arteries. In

non-pregnant women and in early pregnancy, blood flow in the uterine arteries typically has a high systolic flow and low diastolic flow, with the presence of an early diastolic 'notch' seen on Doppler ultrasound. In normal pregnancies, as pregnancy progresses, there is an increase in the uterine end-diastolic flow and thus a fall in resistance to flow in early pregnancy. The diastolic notch typically disappears around 18-24 weeks of gestation [16]. The persistence of a diastolic notch beyond 24 weeks of gestation and/or abnormal flow velocity ratios has been associated with inadequate trophoblast invasion [17]. The umbilical flow velocity waveforms before 14 weeks of gestation are characterized by the absence of end-diastolic velocities, but between 12-14 weeks, the end-diastolic velocities develop rapidly, with a similar increase in end-diastolic velocity and drop in resistance to blood flow [16, 18]. Commonly used blood flow resistance indices include the pulsatility index (peak systolic flow minus end diastolic flow divided by mean flow), the resistance index (peak systolic flow minus end diastolic flow divided by peak systolic flow), and the ratio of the peak systolic flow to the end diastolic flow (S/D ratio). Higher values denote a lower diastolic flow, and thus higher resistance. The indices are correlated with each other, especially in normal pregnancies, but there is no strong evidence that any one measure is less error prone than the other [19, 20]. High uterine and umbilical flow resistance and uterine notching have been shown to be predictive of a range of pregnancy complications and adverse fetal outcomes, most notably pre-eclampsia, intrauterine growth restriction (IUGR), and preterm birth [17, 21–25]. There are few known risk factors for high uterine and umbilical artery resistance indices, but studies have found strong support for smoking during pregnancy and parity [26–30].

1.3 Prenatal risk factors

1.3.1 Maternal diabetes, obesity, and gestational weight gain

Maternal diabetes

Diabetes that occurs prior to pregnancy is either Type 1 or Type 2 diabetes and is diagnosed if any of the following criteria are met or exceeded: 1) random blood glucose level of 200 mg/dL and presence of diabetes symptoms; 2) fasting plasma glucose level of 126 mg/dL after 8-hr fast; 3) 2-hr 75-g oral glucose tolerance test equal to or greater than 200 mg/d; or 4) hemoglobin A1C level of 6.5%. Gestational diabetes is the onset of diabetes during pregnancy and is typically tested at 24-28 weeks of pregnancy. If an individual has risk factors for diabetes, then they will be tested at the first prenatal visit for undiagnosed type 2 diabetes. Gestational diabetes is diagnosed using a 75-g oral glucose tolerance test when fasting plasma glucose levels meet or exceed 92 mg/dL at fasting or 180 mg/dL at 1-hr or 153 mg/dL at 2-hr. A 2-step diagnosis strategy can also be used with a 50-g glucose load test at 1h followed by a 3-h 100-g oral glucose tolerance test [31].

The prevalence of pre-pregnancy diabetes in women of reproductive age in California is estimated to be about 2.7%, with the highest prevalence being in Hispanic women at 4.0% [32]. Gestational diabetes affects roughly 7% of pregnancies in California with older women, Asian/Pacific islander women, and multiparous women having the highest rates [33]. Rates of pre-pregnancy diabetes deliveries have increased in California, with a 24% increase from 0.68 per 100 births to 0.84 per 100 births in 2000-2010. Rates of gestational diabetes deliveries also increased by 66% during this same time period, from 4.10 per 100 births to 6.80 per 100 births [34, 35].

The most common fetal outcomes associated with maternal diabetes are macrosomia [defined as birthweight >4000g], large for gestational age births, congenital malformations, and hypoxia. Long-term outcomes for offspring of diabetic mothers include increased risk of diabetes, obesity, and neuropsychological deficits. The frequency and severity of these outcomes are dependent on the degree of glycemic control during gestation though the prevalence of adverse neonatal outcomes appears to be higher for women born with type 1 diabetes than those with gestational diabetes [36–38].

Maternal weight

A commonly used metric of pre-pregnancy weight that has been shown to be predictive of a range of pregnancy complications and adverse fetal outcomes is pre-pregnancy body mass index (BMI) [39]. BMI is defined as weight in kilograms divided by the square of the height in meters and is classified into the following categories by the World Health Organization (WHO): <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), ≥30 (obese) [40]. The estimated prevalence of women aged 18-44 who were overweight or obese in California is 26% and 22%, respectively. Rates of obesity among women giving birth in California between 1999 and 2005 increased by 55% from 0.84% to 1.3%, with the largest increase among Hispanics (80%) [32, 41].

Given the increasing rates of women entering pregnancy as overweight or obese and the increased risk of excessive weight gain during pregnancy for obese women, new guidelines for the recommended amount of weight gain during pregnancy were issued by the Institute of Medicine (IOM) in 2009 [42, 43]. They specified the following total amount of weight gain by the mother's pre-pregnancy BMI category: 12.5-18 kg in underweight women, 11.5-16 kg in normal weight women, 7-11.5 kg in overweight women, and 5-9 kg in obese women. Women

who gain below their recommended amount of weight gain are defined as having inadequate gestational weight gain (GWG), whereas women who exceed their recommended amount are said to have excessive GWG [43].

The adverse perinatal and childhood outcomes associated with maternal pre-pregnancy BMI and GWG are similar. Studies have shown that maternal obesity and excessive GWG exert independent influences on newborn health, most consistently shown is an increased risk of preterm births, macrosomia, and large for gestational age births. Overall associations are stronger for pre-pregnancy obesity than for excessive GWG. Additionally, studies have found that maternal obesity increases the risk of fetal death and congenital anomalies. The long-term consequences for children born to mothers with pre-pregnancy obesity and excessive GWG are increased risks of childhood obesity, type 2 diabetes, cardiovascular disease, impaired cognitive function, and respiratory-related outcomes such as childhood asthma [42, 44–46].

In contrast, in mothers who are underweight prior to pregnancy or have inadequate GWG, there is an increased risk of preterm birth, low birthweight, and small for gestational age births [46–49]. Long-term effects in offspring include increased risks of diabetes, obesity, and cardiovascular disease [50].

The effects of gestational weight gain on fetal outcomes may also partially depend on the timing of weight gain during pregnancy as GWG during early pregnancy reflects more maternal fat deposition whereas in mid and late pregnancy it reflects maternal and amniotic fluid expansion, and growth of the fetus, placenta, and uterus. Studies have shown that mid- and late weight gain are more associated with birthweight whereas early weight gain is more associated with childhood obesity and cardio-metabolic outcomes [45].

Maternal BMI and GWG are also related to maternal diabetes, with obese mothers and mothers who gain excessive GWG having a higher prevalence of pre-pregnancy diabetes or being more likely to develop gestational diabetes [38, 42, 44, 45].

Maternal diabetes and childhood cancers

A population-based cohort study in Denmark, which grouped together all cancer types, found an increased risk of any malignant neoplasm in children prenatally exposed to type 2 diabetes (OR=2.2) whereas results for type 1 diabetes were attenuated (OR=1.3) and no association was found with gestational diabetes (OR=0.7, 95%CI: 0.4-1.3) [51]. A Swedish population-based study that also looked at any malignant neoplasm in relation to type 1 diabetes found an increased risk (OR=2.25) [52].

Studies examining specific cancer types found elevated risks of leukemia (OR=1.4, OR=2.1), NHL (OR=1.79), and Hodgkin's lymphoma with pre-pregnancy diabetes (OR=1.45), but no associations for hepatoblastoma (OR=0.93) and retinoblastoma (OR=0.86) [53–57]. These studies were all registry-based studies and none differentiated between type 1 and type 2 diabetes. Furthermore, many studies also failed to distinguish between pre-pregnancy and gestational diabetes. Studies that looked at any maternal diabetes have found varying results for several cancer types. For leukemia, one study found an increased risk (OR=1.44) and another found no association (OR=1.00) [58, 59]. The evidence for neuroblastoma is also inconclusive with one study finding an elevated risk (OR=1.71), but another finding a weaker association (OR=1.1) [60, 61]. For retinoblastoma, one study found a trend towards a positive association for unilateral and bilateral retinoblastoma (OR=1.9, OR=2.2, respectively) [54].

Studies have consistently found an increased risk of leukemia (OR=1.7, OR= 2.99, OR=2.3) in offspring of mothers with gestational diabetes [53, 62, 63]. One study that examined neuroblastoma found a positive association (OR=1.84) whereas another looking at hepatoblastoma found no suggestion of an increased risk (OR=0.79, 95% CI: 0.43-1.48) [60, 64].

Pre-pregnancy BMI and childhood cancers

Studies that have examined underweight pre-pregnancy BMI in relation to childhood cancers have found an increased risk of brain tumors (OR=1.8), unilateral and bilateral retinoblastoma (OR=2.6, 4.5, respectively), and hepatoblastoma (OR=1.4) [54, 65, 66]. Though many studies have also found increased risks of retinoblastoma (OR=1.2), hepatoblastoma (OR=2.9), and leukemia with a pre-pregnancy BMI of overweight (OR=1.61), these effects estimates are attenuated or null in the obese group [54, 66, 67]. Thus, these associations could be spurious or may reflect an increased risk of competing outcomes such as fetal death that has been observed with maternal obesity [68]. One study that examined the relation between a BMI of overweight or obese found an increased risk with leukemia (OR=1.44), and two other studies that looked at maternal BMI as a continuous variable found null associations with all childhood cancers and hepatoblastoma [58, 64, 69].

Gestational weight gain and childhood cancers

Many studies have examined weight gain during pregnancy in terms of arbitrary cutoffs that may not accurately reflect risk and that are likely to have produced the inconclusive findings in the literature [53, 58, 59, 64, 66, 67]. Only two studies have used the IOM guidelines for appropriate GWG, with one study finding an increased risk of brain tumors with inadequate (OR=1.8) and excessive (OR=1.4) weight gain, whereas the other study on retinoblastoma found no associations [54, 65].

1.3.2 Hispanic enclaves

Enclaves or ghettos are conceptualized as neighborhoods in which a particular population group, self-defined by ethnicity, race, religion or some other characteristic, is found in high proportions [70, 71]. However, these terms have distinct connotations because they are thought to arise from different social processes. Enclaves are formed voluntarily by members of a particular population group as a means of protecting and enhancing their economic, political, or cultural development [70, 72]. In contrast, ghettos are produced by restriction on residential choice brought about by discriminatory housing practices. Though the ban of these practices by the Fair Housing Act in 1968 makes it more likely that people living in areas with a high concentration of their own race/ethnicity are doing so by choice, their choices might be restricted by financial resources, location of employment, and the continuance of discriminatory practices by realtors ("redlining") [70]. Areas with a high concentration of Hispanics will be henceforth referred to as enclaves in this paper, but in reality these terms do not capture the fact that many spatial patterns are formed by a combination of both of these processes [72].

The spatial assimilation theory states that when immigrants arrive in the US they tend to settle together, but as they achieve greater economic and social resources and acculturate, they leave their ethnic enclaves for more ethnically mixed neighborhoods. Studies have found that Mexican immigrants seem to follow this pattern, whereby as Mexican immigrants gain more choices (higher income, homeowners, not working in ethnic sectors), they are less likely to live in more highly concentrated Mexican neighborhoods [73]. Studies have also reported that Hispanics who live in these enclaves are more socially integrated, have larger and more diverse social networks, and exhibit a lower prevalence of negative health behaviors, such as smoking

during pregnancy [74, 75]. The health advantage conferred by living in these enclaves is expected to persist despite the typically greater socioeconomic disadvantage of mothers living in these enclaves. Consequently, Hispanic enclaves may be a proxy measure of acculturation which can have important implications for health outcomes.

Literature on Hispanic enclaves and childhood cancer risk

While studies of adults have found that living in Hispanic enclaves is associated with increased risk of liver, gastric, and cervical cancers -infectious disease related cancers-- but decreased risk of breast, colorectal, lung, Hodgkin lymphoma, and prostate cancers –lifestyle-related cancers-- among Hispanic adults, no study to date has investigated childhood cancer [76–81]. However, studies have looked at a number of perinatal risk factors (maternal smoking during pregnancy and gestational diabetes) and outcomes (birthweight, preterm birth) [82, 83]. The findings of these studies are inconclusive and most did not explore variations by maternal nativity. The definitions of enclaves and neighborhoods vary substantially between studies even for those examining the same health risk factor or outcome. This makes the interpretation of results across studies difficult since it is unclear whether differences in results are attributable to the definitions used. Although there is no accepted definition of a neighborhood, many studies identify neighborhoods as census tracts or block groups due to ease of accessibility of these data. The major limitation with this approach is that these administrative areas are poor proxies for what participants may think of as their "neighborhood" [84]. The use of census tracts as a measure of neighborhood is often justified by the fact that they were developed to be homogenous with respect to socioeconomic characteristics and thus their characteristics may correlate well with what people consider to be their neighborhood [85]. However, the spatial

scale that is relevant may vary by a specific health outcome, and may also not coincide with what a person thinks of as their "neighborhood"[84].

In terms of measures of Hispanic enclaves, many studies have relied on the proportion of Hispanics or Hispanic foreign-born in a neighborhood. Authors either treated it as a continuous measure or identified a certain threshold above which that neighborhood is considered a Hispanic enclave (typically >25-50%). No studies to date have assessed whether any one measure is a better construct of enclaves. Other California studies on Hispanic enclaves which examined adult cancers used California Cancer Registry data and relied on either census tract or block groups as their measure of neighborhood size. They all used the same measure of Hispanic enclaves, which is a composite index derived using principal component analysis that includes the following variables: % of Hispanic residents foreign-born, recent immigrants, linguistically isolated households, Spanish language speaking households that are linguistically isolated, and all language speakers with limited English proficiency. This index is comprehensive in that includes commonly used measures of acculturation (ie. place of birth, language, time spent in the US) [86, 87].

1.3.3 Traffic-related air pollution

Air pollution exposure assessment

The effect of air pollution in relation to pregnancy complications and adverse birth outcomes has been mainly studied using measures of ambient exposure: the pollutant concentration at maternal address at birth estimated with environmental models (land-use regressions or dispersion) or air pollutant data from air pollution monitoring stations closest to maternal residence at time of birth, as well as cruder metrics such as traffic density [88]. Studies typically examine the following criteria air pollutants: particulate matter, nitrogen oxides, carbon

monoxide, sulfur dioxide, or ozone. Few studies have used personal air monitoring data, which may better capture the differences in women's activity patterns (time spend indoors vs outdoors) [89, 90]. The interpretation of results across studies is complicated not only by the measurement methods employed, but also differences in the number and type of pollutants considered, the pregnancy exposure windows considered, and inconsistencies in exposure categories/scaling [91].

Air monitors allow estimation of community-wide average exposure, but they may not adequately capture spatial variations in air pollutant levels thus providing lower quality data for spatially heterogeneous pollutants such as carbon monoxide (CO). They are most useful in assessing variation of pollutant levels over time. Land use regression or dispersion models use various geographic information systems (GIS) to predict measured concentrations of a pollutant at a given location. These models are limited by the inputs of the data and are also meant to characterize spatial rather than temporal variability in air pollution levels [88, 91]. Personal monitoring and biomarkers may help to address the issue of exposure misclassification due to residential mobility during pregnancy as well as activity patterns. However, some limitations of these methods include the associated costs, labor, and difficulty in determining which pollutant to measure [90, 91].

The variability in air pollutants considered as well as the collinearity between these pollutants is another major issue in exposure assessment. It may be difficult to identify which pollutant is the harmful agent due to the correlation of pollutants in space and time, and assessment is further complicated by the fact that not every pollutant may be measured at every station in a given region and the potential synergistic effects from pollutant mixtures [89, 92].

The evidence on which exposure windows during pregnancy are most susceptible to the effects of air pollution is largely inconclusive. Based on the existing literature, the first and third trimester air pollution exposures have been implicated as having the most relevance for birth outcomes, particularly for preterm birth and low birthweight [89, 92].

Literature on prenatal air pollution exposure and placental vascular resistance

To date air pollution has been most consistently associated with pregnancy-induced hypertensive disorders, low birthweight, and small for gestational age and preterm births [88, 89]. Studies on air pollution in relation to placental vascular resistance are limited, however, with only two studies to date [90, 93]. One study in Brazil measured nitrogen dioxide (NO_2) and ozone (O_3) exposure in pregnancy women once each trimester using a passive personal sampler. Doppler ultrasound was used to assess uterine and umbilical pulsatility resistance indices in all three trimesters. They found that higher levels of O_3 during the 2nd trimester were associated with higher umbilical artery pulsatility indices, but paradoxically higher levels during the 3rd trimester were associated with lower pulsatility. No associations were for the uterine artery [90]. The other study was conducted in the Netherlands and assessed exposure to particulate matter 10 (PM_{10}) and NO_2 during pregnancy at the home address of the mother using continuous monitoring data and dispersion modeling techniques, taking into account both spatial and temporal variation in air pollution. Different windows of exposure assessment in pregnancy were used: 2 weeks before outcome measurement, 2 months before outcome measurement, and averaged over the pregnancy period from conception until outcome measurement. This study examined umbilical and uterine artery pulsatility indices in the second and third trimester as well as uterine notching in the third trimester for these different exposure windows. They found no associations between

umbilical and uterine pulsatility resistance indices and PM_{10} and NO_2 exposure in the second and third trimester, but did find an association between NO_2 exposure and 3rd-trimester uterine bilateral notching [93].

1.3.4 Maternal smoking

Epidemiology

From 2000 to 2010 based on data from 40 US states, not including California, the prevalence of smoking during pregnancy decreased from 13.3% in 2000 to 12.3% in 2010 and the percentage of women who quit during pregnancy increased from 43.2% to 54.3% [94]. However, the prevalence of smoking during the 3 months prior to pregnancy did not change from 2000 to 2010 with a prevalence of about 23%. California has lower smoking rates than those reported nationally, with 1.8% of women in 2014 reporting smoking anytime during pregnancy compared to 8.4% of women reporting smoking during pregnancy. Furthermore, about 31% of women reported quitting smoking during pregnancy in California compared to 26% nationally in 2014. Non-Hispanic American Indian or Alaska Native women have the highest rates of smoking prior to and during pregnancy followed by White women. Asian women have the highest rates of quitting prior to or during pregnancy followed by Hispanic women [94]. Information on maternal smoking is typically obtained via self-report, thus it is difficult to get valid estimates due to misreporting of smoking. One study that used urinary cotinine measurements to assess smoking in a sample of US pregnant women found that 24% of active smokers were misclassified as quitters because they inaccurately reported that they had quit or relapsed by mid-pregnancy. Furthermore, women who reported quitting during pregnancy were more likely to have been misclassified than those reporting quitting prior to pregnancy [95].

Literature review on maternal smoking in relation to placental vascular resistance

The effects of maternal smoking on pregnancy complications and birth outcomes have been studied extensively, with strong evidence existing for an increased risk of the following conditions: fetal growth restriction, preterm birth, stillbirth, and pregnancy complications, placental abruption, placenta previa, spontaneous abortions, and ectopic pregnancies [96]. Various studies have also examined the effect of smoking on placental vascular resistance yet there remains no consensus on which vascular beds of the placenta are affected [26]. Additionally, since smoking is subject to misreporting, misclassification of exposure may contribute to variation in study results. Overall, most studies have reported an increase in umbilical and uterine resistance indices with exposure to smoking, with stronger support for an increase in umbilical resistance [26–29, 97–100]. Most of these studies were limited to examination of second and third trimester estimates, thus of the few that examined it, none reported increased resistance in the first trimester. Additionally, few studies have used objective measurements of smoking. One of the two studies that used cotinine and carbon monoxide concentration in exhaled air, found increases in both umbilical and uterine artery resistance in the third trimester [29]. Another that used serum cotinine concentrations and only examined umbilical resistance found an increased risk of high resistance in the second trimester [98].

Chapter 2. Study 1: Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of childhood cancer

2.1 Abstract

Purpose: We aimed to examine the influence of pre-pregnancy diabetes, pre-pregnancy body mass index, 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 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.

2.2 Introduction

It is estimated that 10,380 new childhood cancer cases and 1,250 deaths will occur in the US alone in 2016 [5]. 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 [101]. 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 [13].

Many studies have consistently reported higher birthweights with an increased risk of leukemia, particularly for ALL [69, 102, 103]. Several population-based studies have reported that increasing birthweight may also increase the risk of other childhood cancers, such as Wilms' tumor, CNS tumors, soft tissue sarcomas, neuroblastomas, lymphomas, germ cell tumors, and malignant melanomas [69, 104, 105]. 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 [102, 103, 105].

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 [106–108]. 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 [107, 109]. 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 [110]. 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 [111].

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 [52–54, 57–59, 62–67, 69]. 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 [112–116]. 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 [48, 112, 113]. 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 [32, 34, 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.

2.3 Methods

Study population

This study includes children from the Air Pollution and Childhood Cancers (APCC) study [117]. 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. Based on reports of residential mobility in California, 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 [118]. 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 [14] and potentially related to pregnancy-related characteristics, including maternal obesity [119]. 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 [120]: 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).

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 [92]) and gestational age, based on date of last menses. Size for gestational age was defined as small if birthweight was less than the 10th percentile and as large if it was greater than the 90th percentile of the birthweight standards for a given gestational age, using the method of Alexander and colleagues [121]. The 10th and 90th 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 WHO criteria. 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 IOM 2009 guidelines on optimal weight gain during pregnancy. Socioeconomic status was assessed with a census-based index that has been previously described 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 [122].

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. 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. Parental age and race/ethnicity have been shown to be consistently associated with childhood cancers so these were included in our models. Birthweight was not included because it is a potential mediator between these maternal conditions and childhood cancers. 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. 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+). 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 socioeconomic status (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 [123]. 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).

2.4 Results

Sociodemographic characteristics for cases and controls for the entire study period are shown in Table 2.1, along with their distribution for specific cancer types in Appendix Table A 2.1. We also report sociodemographic characteristics for cases and controls born 2006 and onwards in Appendix Table A 2.2 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 2.2).

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 2.3).

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 2.3, Appendix Table A 2.3).

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 2.3). 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] (Appendix Table A 2.3).

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).

2.5 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)[53, 58], except for one study that failed to find any association (OR=1.00) [59]. 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 [53, 62, 63], and others have found no associations with hepatoblastoma and retinoblastoma [54, 64]. 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 [124]. 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 [38]. Maternal hyperglycemia increases fetal growth, alters fetal metabolism, and induces oxidative stress and epigenetic changes [113, 125, 126]. 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 [52, 54, 64–67, 69]. 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 [54, 67]. 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 [68]. 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 [113].

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 [52, 53, 59, 64, 66, 67]. 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 [65]. 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 [127]. 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 [128], while pre-pregnancy diabetes and gestational diabetes typically have low sensitivity and high specificity [129]. 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 [130]. A Pennsylvania study showed that agreement between pregnancy weight gain on birth records compared to 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 [131]. 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 [132]. 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.

2.6 Tables

Table 2.1 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)
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 2.2 Maternal and perinatal characteristics of cases and controls, birth years 1988-2011												
	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytoma n (%)	Intracranial n (%)	Germ cell	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms 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 term)	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)
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)
≥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)
Gestational weight gain (IOM 2009												
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 2.3. 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		Astrocytoma		Intracranial		Germ cell	
	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	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)
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	---
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)
18.5-<25	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)
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)
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)
IOM recommended	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
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)

[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

Table 2.3 continued…

	Hepatoblastoma		Neuroblastoma		Retinoblastoma		Rhabdomyosarcoma		Wilms'	
	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]
Birth years 1983-2011										
Pre-pregnancy diabetes										
Yes	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	1.65	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	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
25-<30	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+	1.13	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	0.87	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
Too much	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

2.8 Appendix

Table A 2.1. Sociodemographic characteristics of specific childhood cancer types and controls, birth years 1988-2011

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytoma n (%)	Intracranial n (%)	Germ cell n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinoblastoma n (%)	Rhabdomyosarcoma n (%)	Wilms n (%)
n	270147	5034	4101	706	990	709	445	337	1378	741	463	1052
Child sex												
Male	137903 (51.1)	2761 (54.9)	2273 (55.4)	365 (51.7)	534 (53.9)	431 (60.8)	254 (57.1)	202 (59.9)	770 (55.9)	407 (54.9)	279 (60.3)	497 (47.2)
Female	132244 (49.0)	2273 (45.2)	1828 (44.6)	341 (48.3)	456 (46.1)	278 (39.2)	191 (42.9)	135 (40.1)	608 (44.1)	334 (45.1)	184 (39.7)	555 (52.8)
Maternal age at birth												
<20	28520 (10.6)	470 (9.3)	382 (9.3)	72 (10.2)	95 (9.6)	76 (10.7)	53 (11.9)	45 (13.4)	131 (9.5)	71 (9.6)	39 (8.4)	103 (9.8)
20-29	140146 (51.9)	2512 (49.9)	2076 (50.6)	337 (47.7)	498 (50.3)	367 (51.8)	217 (48.8)	137 (40.7)	690 (50.1)	402 (54.3)	240 (51.8)	514 (48.9)
30-34	62952 (23.3)	1206 (24.0)	985 (24.0)	159 (22.5)	249 (25.2)	161 (22.7)	105 (23.6)	83 (24.6)	366 (26.6)	162 (21.9)	117 (25.3)	294 (28.0)
35+	38479 (14.2)	845 (16.8)	658 (16.0)	138 (19.6)	148 (15.0)	105 (14.8)	70 (15.7)	72 (21.4)	191 (13.9)	106 (14.3)	67 (14.5)	140 (13.3)
Missing	50 (0.02)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Father's age												
<20	10331 (3.8)	160 (3.2)	132 (3.2)	22 (3.1)	31 (3.1)	27 (3.8)	13 (2.9)	10 (3.0)	43 (3.1)	24 (3.2)	16 (3.5)	34 (3.2)
20-29	111645 (41.3)	2033 (40.4)	1670 (40.7)	283 (40.1)	394 (39.8)	288 (40.6)	182 (40.9)	136 (40.4)	536 (38.9)	291 (39.3)	185 (40.0)	446 (42.4)
30-34	64765 (24.0)	1251 (24.9)	1046 (25.5)	155 (22.0)	254 (25.7)	192 (27.1)	105 (23.6)	85 (25.2)	366 (26.6)	178 (24.0)	110 (23.8)	252 (24.0)
35+	65683 (24.3)	1347 (26.8)	1058 (25.8)	210 (29.8)	254 (25.7)	156 (22.0)	116 (26.1)	90 (26.7)	362 (26.3)	212 (28.6)	125 (27.0)	265 (25.2)

Missing	17723 (6.6)	243 (4.8)	195 (4.8)	36 (5.1)	57 (5.8)	46 (6.5)	29 (6.5)	16 (4.8)	71 (5.2)	36 (4.9)	27 (5.8)	55 (5.2)
Mother race/ethnicity												
White non-Hispanic	94660 (35.0)	1782 (35.4)	1460 (35.6)	242 (34.3)	506 (51.1)	304 (42.9)	142 (31.9)	113 (33.5)	652 (47.3)	235 (31.7)	181 (39.1)	449 (42.7)
Hispanic of any race	123975 (45.9)	2480 (49.3)	2044 (49.8)	325 (46.0)	335 (33.8)	302 (42.6)	190 (42.7)	169 (50.2)	484 (35.1)	348 (50.0)	192 (41.5)	438 (41.6)
Other/not specified	51512 (19.1)	772 (15.3)	597 (14.6)	139 (19.7)	149 (15.1)	103 (14.5)	113 (25.4)	55 (16.3)	242 (17.6)	158 (21.3)	90 (19.4)	165 (15.7)
Father's race/ethnicity												
White non-Hispanic	83101 (30.8)	1703 (33.8)	1437 (35.0)	201 (28.5)	442 (44.7)	267 (37.7)	121 (27.2)	99 (29.4)	556 (40.4)	218 (29.4)	172 (37.2)	400 (38.0)
Hispanic of any race	117684 (43.6)	2347 (46.6)	1933 (47.1)	307 (43.5)	329 (33.2)	288 (40.6)	181 (40.7)	162 (48.1)	454 (33.0)	336 (45.3)	177 (38.2)	413 (39.3)
Other/not specified	69362 (25.7)	984 (19.6)	731 (17.8)	198 (28.1)	219 (22.1)	154 (21.7)	143 (32.1)	76 (22.6)	368 (26.7)	187 (25.2)	114 (24.6)	239 (22.7)
Maternal Education[a]												
8 or less years	29283 (12.4)	568 (13.0)	457 (12.9)	79 (12.7)	73 (8.6)	65 (10.6)	58 (14.4)	40 (12.9)	95 (7.7)	71 (10.3)	42 (10.7)	86 (9.8)
9-11 years	42758 (18.1)	738 (16.9)	609 (17.2)	97 (15.5)	124 (14.5)	123 (20.1)	70 (17.4)	51 (16.5)	180 (14.6)	132 (19.2)	62 (15.7)	133 (15.1)
12 years	65640 (27.8)	1274 (29.3)	1027 (29.1)	196 (31.4)	248 (29.0)	156 (25.5)	116 (28.9)	88 (28.5)	358 (29.1)	197 (28.6)	112 (28.4)	285 (32.4)
13 to 15 years	47105 (19.9)	835 (19.2)	673 (19.1)	119 (19.1)	197 (23.1)	113 (18.4)	74 (18.4)	43 (13.9)	259 (21.0)	143 (20.8)	75 (19.0)	181 (20.6)
16 or more years	47137 (20.0)	868 (19.9)	709 (20.1)	123 (19.7)	203 (23.8)	147 (24.0)	73 (18.2)	81 (26.2)	312 (25.4)	133 (19.3)	92 (23.4)	184 (20.9)
Missing	4411 (1.9)	73 (1.7)	57 (1.6)	10 (1.6)	9 (1.1)	9 (1.5)	11 (2.7)	6 (1.9)	27 (2.2)	12 (1.7)	11 (2.8)	11 (1.3)
Paternal Education[a]												

8 or less years	29845 (12.6)	596 (13.7)	476 (13.5)	85 (13.6)	80 (9.4)	59 (9.6)	51 (12.7)	36 (11.7)	103 (8.4)	78 (11.3)	33 (8.4)	87 (9.9)
9-11 years	33292 (14.1)	603 (13.8)	483 (13.7)	96 (15.4)	86 (10.1)	69 (11.3)	49 (12.2)	43 (13.9)	143 (11.6)	99 (14.4)	61 (15.5)	114 (13.0)
12 years	65536 (27.7)	1210 (27.8)	980 (27.8)	177 (28.4)	244 (28.6)	171 (27.9)	111 (27.6)	80 (25.9)	364 (29.6)	202 (29.4)	112 (28.4)	273 (31.0)
13 to 15 years	39220 (16.6)	705 (16.2)	584 (16.5)	90 (14.4)	162 (19.0)	125 (20.4)	64 (15.9)	55 (17.8)	229 (18.6)	111 (16.1)	72 (18.3)	161 (18.3)
16 or more years	48540 (20.5)	938 (21.5)	765 (21.7)	133 (21.3)	228 (26.7)	140 (22.8)	87 (21.6)	71 (23.0)	306 (24.9)	149 (21.7)	85 (21.6)	180 (20.5)
Missing	19901 (8.4)	304 (7.0)	244 (6.9)	43 (7.0)	54 (6.3)	49 (8.0)	40 (10.0)	24 (7.8)	86 (7.0)	49 (7.1)	31 (7.9)	65 (7.4)
Source of payment for prenatal care[a]												
Private	116717 (49.4)	2340 (53.7)	1927 (54.6)	317 (50.8)	510 (59.7)	337 (55.0)	208 (51.7)	163 (52.8)	717 (58.3)	354 (51.5)	217 (55.1)	486 (55.2)
Medi-Cal/other governmental/self-pay	116935 (49.5)	1983 (45.5)	1577 (44.7)	306 (49.0)	338 (39.6)	271 (44.2)	193 (48.0)	145 (46.9)	504 (40.9)	328 (47.7)	172 (43.7)	389 (44.2)
Missing	2682 (1.1)	33 (0.8)	28 (0.8)	1 (0.2)	6 (0.7)	5 (0.8)	1 (0.3)	1 (0.3)	10 (0.8)	6 (0.9)	5 (1.3)	5 (0.6)
Census-based SES												
1 (lowest)	67375 (24.9)	1210 (24.0)	977 (23.8)	174 (24.7)	214 (21.6)	153 (21.6)	104 (23.4)	79 (23.4)	275 (20.0)	178 (24.0)	114 (24.6)	244 (23.2)
2	65424 (24.2)	1253 (24.9)	1024 (25.0)	171 (24.2)	239 (24.1)	167 (23.6)	120 (27.0)	64 (19.0)	332 (24.1)	184 (24.8)	112 (24.2)	270 (25.7)
3	59729 (22.1)	1117 (22.2)	923 (22.5)	143 (20.3)	212 (21.4)	180 (25.4)	91 (20.5)	79 (23.4)	331 (24.0)	159 (21.5)	105 (22.7)	221 (21.0)
4	42568 (15.8)	803 (16.0)	647 (15.8)	126 (17.8)	169 (17.1)	120 (16.9)	65 (14.6)	57 (16.9)	231 (16.8)	132 (17.8)	55 (11.9)	174 (16.5)

5 (highest)	34279 (12.7)	642 (12.8)	523 (12.8)	90 (12.8)	156 (15.8)	89 (12.6)	65 (14.6)	58 (17.2)	205 (14.9)	85 (11.5)	77 (16.6)	143 (13.6)
Missing	772 (0.3)	9 (0.2)	7 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)

[a]Collected starting 1989

Table A 2.2. Sociodemographic characteristics of specific childhood cancer types and controls, birth years 2006-2011

	Controls n (%)	Leukemia n (%)	ALL n (%)	AML n (%)	Astrocytoma n (%)	Intracranial n (%)	Germ cell n (%)	Hepatoblastoma n (%)	Neuroblastoma n (%)	Retinolastoma n (%)	Rhabdomyosarcoma n (%)	Wilms n (%)
n	51800	652	429	167	147	124	90	94	294	159	85	193
Child sex												
Male	26560 (51.3)	330 (50.6)	222 (51.8)	79 (47.3)	80 (54.4)	75 (60.5)	58 (64.4)	56 (59.6)	148 (50.3)	85 (53.5)	48 (56.5)	98 (50.8)
Female	25,240 (48.7)	322 (49.4)	207 (48.3)	88 (52.7)	67 (45.6)	49 (39.5)	32 (35.6)	38 (40.4)	146 (49.7)	74 (46.5)	37 (43.5)	95 (49.2)
Maternal age at birth												
<20	4783 (9.2)	58 (8.9)	35 (8.2)	18 (10.8)	12 (8.2)	10 (8.1)	9 (10.0)	10 (10.6)	26 (8.8)	8 (5.0)	7 (8.2)	19 (9.8)
20-29	25168 (48.6)	300 (46.0)	206 (48.0)	76 (45.5)	68 (46.3)	53 (42.7)	40 (44.4)	36 (38.3)	142 (48.3)	85 (53.5)	43 (50.6)	98 (50.8)
30-34	12675 (24.5)	151 (23.2)	102 (23.8)	32 (19.2)	36 (24.5)	41 (33.1)	18 (20.0)	26 (27.7)	78 (26.5)	44 (27.7)	22 (25.9)	47 (24.4)
35+	9165 (17.7)	143 (21.9)	86 (20.1)	41 (24.6)	31 (21.1)	20 (16.1)	23 (25.6)	22 (23.4)	48 (16.3)	22 (13.8)	13 (15.3)	29 (15.0)
Missing	9 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Father's age												
<20	1913 (3.7)	21 (3.2)	11 (2.6)	8 (4.8)	6 (4.1)	6 (4.8)	2 (2.2)	2 (2.1)	11 (3.7)	3 (1.9)	3 (3.5)	6 (3.1)
20-29	19398 (37.5)	225 (34.5)	153 (35.7)	59 (35.3)	57 (38.8)	42 (33.9)	32 (35.6)	42 (44.7)	106 (36.1)	57 (35.9)	34 (40.0)	72 (37.3)
30-34	12129 (23.4)	159 (24.4)	107 (24.9)	39 (23.4)	31 (21.1)	41 (33.1)	19 (21.1)	21 (22.3)	76 (25.9)	34 (21.4)	20 (23.5)	46 (23.8)
35+	14613 (28.2)	203 (31.1)	125 (29.1)	52 (31.1)	41 (27.9)	27 (21.8)	30 (33.3)	24 (25.5)	83 (28.2)	53 (33.3)	25 (29.4)	54 (28.0)
Missing	3747 (7.2)	44 (6.8)	33 (7.7)	9 (5.4)	12 (8.2)	8 (6.5)	7 (7.8)	5 (5.3)	18 (6.1)	12 (7.6)	3 (3.5)	15 (7.8)

Mother race/ethnicity												
White non-Hispanic	14009 (27.0)	186 (28.5)	113 (26.3)	53 (31.8)	68 (46.3)	40 (32.3)	18 (20.0)	21 (22.3)	106 (36.1)	34 (21.4)	26 (30.6)	66 (34.2)
Hispanic of any race	26917 (52.0)	356 (54.6)	241 (56.2)	86 (51.5)	56 (38.1)	61 (49.2)	47 (52.2)	50 (53.2)	123 (41.8)	86 (54.1)	43 (50.6)	99 (51.3)
Other/not specified	10874 (20.1)	110 (16.9)	75 (17.5)	28 (16.8)	23 (15.7)	23 (18.6)	25 (27.8)	23 (24.5)	65 (22.1)	39 (24.5)	16 (18.8)	28 (14.5)
Father's race/ethnicity												
White non-Hispanic	6250 (12.1)	113 (17.3)	82 (19.1)	24 (14.4)	26 (17.7)	19 (15.3)	9 (10.0)	7 (7.5)	36 (12.2)	13 (8.2)	12 (14.1)	21 (10.9)
Hispanic of any race	24745 (47.8)	320 (49.1)	214 (49.9)	77 (46.1)	59 (40.1)	57 (46.0)	38 (42.2)	47 (50.0)	105 (35.7)	85 (53.5)	36 (42.4)	94 (48.7)
Other/not specified	20805 (40.2)	219 (33.6)	133 (31.0)	66 (39.5)	62 (42.2)	48 (38.7)	43 (47.8)	40 (42.6)	153 (52.0)	61 (38.4)	37 (43.5)	78 (40.4)
Maternal Education[a]												
8 or less years	4523 (8.7)	60 (9.2)	40 (9.3)	11 (6.6)	9 (6.1)	6 (4.8)	12 (13.3)	8 (8.5)	15 (5.1)	16 (10.1)	5 (5.9)	16 (8.3)
9-11 years	9906 (19.1)	119 (18.3)	81 (18.9)	29 (17.4)	24 (16.3)	28 (22.6)	20 (22.2)	16 (17.0)	46 (15.7)	35 (22.0)	16 (18.8)	34 (17.6)
12 years	12271 (23.7)	139 (21.3)	92 (21.5)	36 (21.6)	37 (25.2)	24 (19.4)	23 (25.6)	22 (23.4)	67 (22.8)	36 (22.6)	26 (30.6)	51 (26.4)
13 to 15 years	11269 (21.8)	162 (24.9)	103 (24.0)	43 (25.8)	37 (25.2)	23 (18.6)	21 (23.3)	16 (17.0)	63 (21.4)	31 (19.5)	17 (20.0)	44 (22.8)
16 or more years	12149 (23.5)	151 (23.2)	99 (23.1)	43 (25.8)	37 (25.2)	39 (31.5)	11 (12.2)	27 (28.7)	86 (29.3)	36 (22.6)	16 (18.8)	42 (21.8)
Missing	1682 (3.3)	21 (3.2)	14 (3.3)	5 (3.0)	3 (2.0)	4 (3.2)	3 (3.3)	5 (5.3)	17 (5.8)	5 (3.1)	5 (5.9)	6 (3.1)
Paternal Education[a]												

8 or less years	4876 (9.4)	73 (11.2)	45 (10.5)	18 (10.8)	10 (6.8)	9 (7.3)	8 (8.9)	7 (7.5)	16 (5.4)	13 (8.2)	5 (5.9)	22 (11.4)
9-11 years	8465 (16.3)	99 (15.2)	66 (15.4)	26 (15.6)	17 (11.6)	21 (16.9)	20 (22.2)	15 (16.0)	39 (13.3)	30 (18.9)	15 (17.7)	19 (9.8)
12 years	12471 (24.1)	148 (22.7)	96 (22.4)	38 (22.8)	44 (29.9)	26 (21.0)	21 (23.3)	20 (21.3)	72 (24.5)	37 (23.3)	25 (29.4)	46 (23.8)
13 to 15 years	9286 (17.9	128 (19.6)	85 (19.8)	33 (19.8)	26 (17.7)	30 (24.2)	9 (10.0)	16 (17.0)	65 (22.1)	32 (20.1)	17 (20.0)	46 (23.8)
16 or more years	11116 (21.5)	135 (20.7)	89 (20.8)	37 (22.2)	33 (22.5)	29 (23.4)	19 (21.1)	23 (24.5)	67 (22.8)	29 (18.2)	15 (17.7)	38 (19.7)
Missing	5586 (10.8)	69 (10.6)	48 (11.2)	15 (9.0)	17 (11.6)	9 (7.3)	13 (14.4)	13 (13.8)	35 (11.9)	18 (11.3)	8 (9.4)	22 (11.4)
Source of payment for prenatal care[a]												
Private	24107 (46.5)	330 (50.6)	219 (51.1)	84 (50.3)	82 (55.8)	69 (55.7)	43 (47.8)	47 (50.0)	154 (52.4)	68 (42.3)	41 (48.2)	104 (53.9)
Medi-Cal/other governmental/self-pay	27288 (52.7)	317 (48.6)	207 (48.3)	83 (49.7)	64 (43.5)	55 (44.4)	47 (52.2)	47 (50.0)	138 (46.9)	90 (56.6)	44 (51.8)	88 (45.6)
Missing	405 (0.8)	5 (0.8)	3 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.6)	0 (0.0)	1 (0.5)
Census-based SES												
1 (lowest)	13690 (26.4)	159 (24.4)	103 (24.0)	40 (24.0)	35 (23.8)	26 (21.0)	29 (32.2)	26 (27.7)	58 (19.7)	45 (28.3)	21 (24.7)	46 (23.8)
2	12299 (23.7)	167 (25.6)	111 (25.9)	39 (23.4)	30 (20.4)	25 (20.2)	25 (27.8)	19 (20.2)	66 (22.5)	30 (18.9)	21 (24.7)	60 (31.1)
3	10395 (20.1)	134 (20.6)	94 (21.9)	32 (19.2)	29 (19.7)	35 (28.2)	16 (17.8)	20 (21.3)	70 (23.8)	39 (24.5)	23 (27.1)	28 (14.5)
4	8370 (16.2)	115 (17.6)	70 (16.3)	38 (22.8)	29 (19.7)	20 (16.1)	13 (14.4)	15 (16.0)	51 (17.4)	30 (18.9)	7 (8.2)	33 (17.1)

5 (highest)	6819 (13.2)	75 (11.5)	50 (11.7)	17 (10.2)	24 (16.3)	18 (14.5)	7 (7.8)	14 (14.9)	49 (16.7)	14 (8.8)	13 (15.3)	26 (13.5)
Missing	227 (0.4)	2 (0.3)	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

[a]Collected starting 1989

Table A 2.3. Multiple Imputation analysis: 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	
Birth years 2007-2011										
Pre-pregnancy BMI										
	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]
<18.5	0.66	0.68 (0.33, 1.38)	0.64	0.65 (0.26, 1.59)	0.69	0.71 (0.22, 2.28)	1.06	1.06 (0.38, 2.94)	1.62	1.70 (0.60, 4.84)
18.5-<25	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-<30	1.26	1.26 (1.01, 1.58)	1.20	1.20 (0.89, 1.61)	1.11	1.12 (0.71, 1.75)	1.12	1.24 (0.77, 1.98)	0.93	0.91 (0.54, 1.54)
30+	1.15	1.15 (0.89, 1.50)	1.07	1.07 (0.75, 1.52)	1.07	1.08 (0.64, 1.81)	1.01	1.15 (0.68, 1.97)	0.51	0.49 (0.23, 1.06)
Gestational weight gain (IOM 2009 guidelines)										
Not enough weight	0.90	0.90 (0.69, 1.17)	0.76	0.76 (0.53, 1.08)	1.45	1.43 (0.86, 2.41)	1.18	1.25 (0.71, 2.20)	1.03	1.06 (0.57, 2.00)
IOM recommended	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Too much	0.84	0.84 (0.67, 1.06)	0.84	0.85 (0.64, 1.14)	1.03	1.02 (0.63, 1.65)	1.52	1.49 (0.92, 2.43)	0.70	0.70 (0.43, 1.16)

[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

Table A 2.3 continued…

Birth years 2007-2011

Pre-pregnancy BMI

	Germ cell		Hepatoblastoma		Neuroblastoma		Retinoblastoma		Rhabdomyosarcoma		Wilms'	
	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]	OR[a]	OR (95% CI)[b, c]
<18.5	2.13	2.00 (0.79, 5.09)	1.11	1.07 (0.33, 3.49)	0.91	0.91 (0.42, 1.98)	0.65	0.65 (0.16, 2.59)	1.30	1.39 (0.35, 5.58)	0.26	0.28 (0.04, 1.83)
18.5-<25	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-<30	0.90	0.96 (0.52, 1.77)	0.78	0.80 (0.42, 1.51)	0.98	1.05 (0.76, 1.45)	1.42	1.33 (0.88, 2.01)	0.93	0.93 (0.47, 1.83)	0.80	0.80 (0.52, 1.24)
30+	0.79	0.86 (0.41, 1.81)	1.17	1.20 (0.66, 2.16)	1.06	1.17 (0.82, 1.67)	0.98	0.88 (0.51, 1.49)	1.12	1.14 (0.55, 2.37)	0.78	0.78 (0.48, 1.27)
Gestational weight gain (IOM 2009 guidelines)												
Not enough weight	1.20	1.18 (0.58, 2.42)	0.84	0.83 (0.42, 1.64)	0.75	0.79 (0.54, 1.16)	0.85	0.83 (0.48, 1.46)	0.81	0.85 (0.39, 1.88)	0.89	0.92 (0.59, 1.45)
IOM recommended	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Too much	0.98	1.05 (0.53, 2.10)	1.23	1.31 (0.76, 2.25)	0.97	0.95 (0.70, 1.29)	1.08	1.11 (0.73, 1.70)	1.03	1.01 (0.53, 1.92)	0.84	0.80 (0.55, 1.18)

[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

Chapter 3. Childhood cancer risk in Hispanic enclaves in California

3.1 Abstract

Background: Hispanic enclaves may be a proxy measure of acculturation with those living outside enclaves being more acculturated. Since acculturation in Hispanic women has been associated with negative prenatal behaviors and birth and child health outcomes, we aimed to assess whether living in Hispanic enclaves during pregnancy affects childhood cancer risk among Hispanics.

Methods: Cancer cases (n=6,112) among Hispanic children diagnosed under 6 years of age were identified from the California cancer registry between 1988-2013. Hispanic control children (n=124,401) were randomly selected from California birth records. Data from the US decennial census (1990, 2000), and the American Community Survey (ACS) from 2007-2011 was used to create an index measure of Hispanic enclaves by census tract. Tracts scoring higher on this index can be considered Hispanic enclaves or more enclave-like neighborhoods. Covariate information was obtained from California birth records. In multivariable logistic regression models we estimated the effects of living in Hispanic enclaves on cancer risk among young Hispanic children overall and by maternal nativity.

Results: Offspring of Hispanic mothers living in the least enclave-like neighborhoods were at increased risks of rhabdomyosarcoma [OR=1.57, 95% CI: (1.03, 2.38)], but at reduced risk of acute myeloid leukemia (AML) [OR=0.73, 95% CI: (0.52, 1.03)]. Living in the least enclave-like neighborhoods resulted in lower risks of hepatoblastoma [OR=0.41, 95% CI: 0.17, 0.98] among

offspring of US-born Hispanic mothers and lower risks of retinoblastoma among children of foreign-born Hispanic mothers [OR=0.52, 95% CI: 0.33, 0.83), OR=0.49, 95% CI: 0.27, 0.90)]. When stratifying by regions in California, we found that living in the least-enclave-like neighborhoods in LA county resulted in an elevated risk of ALL and Wilms tumor [OR=1.39, 95% CI: (1.00, 1.93), OR=1.82, 95% CI: (1.05, 3.16), respectively].

Conclusion: Overall residence in Hispanic did not have a uniformly beneficial effect, rather living outside of these enclaves decreased the risk of certain childhood cancers. However, there was substantial variation in risk by maternal nativity status and region of residence in California. These patterns are likely a reflection of distinct distributions of risk factors in these populations. Further investigation of potential risk and preventive factors that characterize Hispanic enclaves is warranted with attention to the mother's country of birth and the region of the enclaves.

3.2 Introduction

The Hispanic Epidemiologic Paradox, whereby Hispanics have been shown to have better or comparable health outcomes as their white counterparts despite experiencing greater socioeconomic disadvantage, has been widely noted in the literature [133]. This health advantage has been shown to extend to perinatal outcomes, particularly among Mexican-origin women [134]. Although much of the literature has focused on differences between Hispanic and white mothers, there is evidence that differences exist among Hispanic women such that worse perinatal outcomes are observed in US-born compared to foreign-born women. For instance, many studies have found that US-born Hispanic mothers have higher rates of low birthweight and preterm births compared with foreign-born Hispanic mothers [135–137]. The health

differential among Hispanic women by birthplace is hypothesized to be related to acculturation. Even though income, education, and access to health care services are higher in second-generation than immigrant mothers, US-born Hispanic women are also more likely to adopt negative health behaviors such as tobacco and alcohol use similar to their white peers, and experience higher levels of stress [134].

One measure of acculturation is residence in Hispanic enclaves, neighborhoods that maintain native cultural practices and are culturally and ethnically distinct from surrounding areas [79]. Spatial assimilation theory states that when immigrants arrive in the US they tend to settle together, but as they achieve greater economic and social resources and acculturate, they leave their ethnic enclaves for more ethnically mixed neighborhoods. Studies reported that Hispanics who live in these enclaves are more socially integrated, have larger and more diverse social networks, and exhibit less prevalence of negative health behaviors, such as smoking during pregnancy [74, 75]. The health advantage conferred by living in these enclaves is expected to persist despite the typically greater socioeconomic disadvantage of mothers living in these enclaves.

Since many childhood cancers are thought to be related to exposures during pregnancy or early infancy, and living in an enclave has been associated with improved health resources and behaviors during pregnancy, it is plausible that living in an ethnic enclave may affect childhood cancer risk. Established risk factors for childhood cancers include ionizing radiation, structural birth defects, certain congenital genetic syndromes, and parental smoking in the case of hepatoblastoma [13, 138].

While studies have found that living in Hispanic enclaves is associated with increased risk of liver, gastric, and cervical cancers but decreased risk of breast, colorectal, lung, Hodgkin

lymphoma, and prostate cancers among Hispanic adults, to our knowledge no study has investigated childhood cancer [76–81]. A recent study by our group showed that Hispanic children were at reduced risk for most CNS tumors, neuroblastoma, and Wilms' tumor compared with whites, and that foreign-born Hispanics exhibited the lowest risk of these cancers [7]. We hypothesize that for these childhood cancers, in which maternal health behaviors seem to play an important role in incidence, living outside of these enclaves will increase the risk of childhood cancers due to poorer health behaviors and reduced social support during pregnancy. Thus, here we hope to elucidate neighborhood factors that may be driving differences in cancer risk among Hispanics, specifically whether residence in a Hispanic enclave affects risk of various cancers in a population-based sample of children born to Hispanic mothers residing in California.

3.3 Methods

This study includes children from the Air Pollution and Childhood Cancers (APCC) study previously described [117]. We linked cancer cases identified from the California Cancer Registry (1988-2013) to California birth records (1983-2011) for children diagnosed at 5 years of age or younger. The APCC study was restricted to young children because perinatal exposures are likely to be most relevant for cancers diagnosed in early childhood. In the parent study, 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. Given the rates of residential mobility in early childhood, it is likely that the children we were unable to match were those who moved to California after birth [118]. Controls were children without a cancer diagnosis before 6 years of age in California. 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 present analysis is limited to children of Hispanic mothers and children born in California. Control children were excluded if they died of any cause prior to age 6 (n=770), were missing sex (n=3), and were likely not viable (gestational age <20 weeks and/or birthweight <500g) (n=89). The final sample included 6,112 cases and 124,401 controls.

Childhood cancer types were classified according to their respective International Classification of Childhood Cancer, 3rd edition (ICCC-3) or International Classification of Diseases for Oncology (ICD-O) codes [120]: leukemias (codes 011-015), acute lymphoblastic leukemia (ALL) (code 011), AML (code 012), non-Hodgkin lymphomas (NHL) (codes 022-023), ependymomas (code 031), astrocytomas (code 032), intracranial and intraspinal embryonal brain tumors (code 033), PNET (code 9473), medulloblastomas (code 9470), neuroblastomas (code 041), retinoblastomas (code 050), Wilms' tumors (code 061), hepatoblastomas (code 071), soft tissue sarcomas (codes 091-095), rhabdomyosarcomas (code 091), germ cell tumors (code 101-105), yolk sac tumors (code 9071), and teratomas (code 9080). We included specific cancer types with at least 65 cases.

Study variables

Covariate information and maternal residential address at child's birth was obtained from California birth certificates. Addresses were geocoded using our open-source geocoder with manual correction of unmatched addresses [139]. Exact home addresses were recorded on electronic birth certificates from 1998. Prior to 1998, only ZIP codes were available, and we geocoded the ZIP code centroid for those children. Children born 1983-1995 were assigned to 1990 census tracts, children born 1996-2006 were assigned to 2000 census tracts, and children born 2007-2011 were assigned to 2011 census tracts. We constructed a neighborhood-level Hispanic enclave index that has been previously used in California cancer registry studies [86]

using US decennial census tract data from 1990 and 2000, and ACS data from 2007-2011 based on the following variables: percent of Hispanic residents foreign-born, recent immigrants, linguistically isolated households, Spanish language speaking households that are linguistically isolated, and all language speakers with limited English proficiency. The enclave measure was then categorized into quintiles based on the distribution of census tracts in California. Neighborhoods that score higher on this index are more characteristic of Hispanic enclaves, which will henceforth be referred to as more enclave-like neighborhoods.

We collapsed quintiles further into three categories in order to increase our sample size with the lowest three quintiles (0-60%) indicating the least enclave-like neighborhoods, quintile 4 indicating intermediate, and the highest quintile indicating the most enclave-like neighborhoods. For our neighborhood-level SES measure, we created an index previously described [122] using the following census tract variables: 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. The SES measure was categorized into quintiles based on the distribution of census tracts in California with higher values indicating a higher SES neighborhood. Our rural/urban place of residence measure was based on 1990, 2000, and 2010 rural-urban commuting area (RUCA) codes used to classify US census tracts [140] . Children were assigned to 1990, 2000, or 2007-2011 census values depending on their tract assignment. For our RUCA measure, since data is not available for 2011 census tracts, children assigned to 2011 census tracts were assigned 2010 values.

Statistical Analyses

Unconditional logistic regression was used to examine the associations between residence in Hispanic enclaves and childhood cancer risk. We used SAS Proc Surveylogistic to account for

clustering at the census tract level. Mixed models were not appropriate for our data as our results indicated random effects were not necessary (ie. variance of random effect was zero, intraclass correlation coefficient=0.006). We also tested using population averaged models using Proc genmod, which are often used as an alternative in neighborhood studies. These models use generalized estimating equations and involve fewer assumptions [141]. Our results for these models were nearly identical to our logistic regression results, thus we opted to use the simpler logistic regression results [Table A 3.1]. We report crude and adjusted odds ratios (OR) and 95% confidence intervals (CI). We adjusted for our matching variable, year of birth, and for individual and neighborhood-level variables that have been associated with childhood cancer risk and that could be associated with neighborhood characteristics: maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age [7, 13, 142]. We also tested the inclusion of the following variables: parental education, maternal race, housing density, parity, multiple birth, urban/rural tract, trimester of prenatal care initiation, and source of payment for prenatal care for each cancer type, but left them out of our main models as they changed effect estimates by <10%. We did not adjust for birthweight in our models as it may be a potential intermediate on the casual pathway. We also conducted analyses stratified by maternal nativity (foreign-born vs US-born) to determine whether effect estimates differ by this factor.

Since exact home address was only collected starting 1998, we conducted sensitivity analyses to assess the effect of living in Hispanic enclaves on childhood cancer risk in this subgroup. We have traffic- related air pollution estimates of CO at the home address for the child's first year for this children born 1998-2007 [143].Thus, we provide models adjusted for this factor as well.

We also conducted sensitivity analyses to assess how each individual variable in our index may be driving any differences in cancer risk by examining the association between each variable our index consisted of and childhood cancers. We categorized each variable similar to the enclave index (lowest three quintiles=low, intermediate=4th quintile, and 5th quintile=high).

We also assessed stratification by the two major regions represented in our sample, Los Angeles County and the Central Valley (Butte, Colusa, Glenn, El Dorado, Fresno, Kings, Madera, Merced, Placer, San Joaquin, Sacramento, Shasta, Stanislaus, Sutter, Tehama, Tulare, Yuba, Yolo, and Kern). We also examined associations only among those living in urban tracts and among Mexican-born mothers only.

3.4 Results

Hispanic mothers who lived in more enclave-like neighborhoods had less years of formal education, were slightly younger, and more likely to be foreign-born as compared with mothers who lived in less enclave-like neighborhoods. Mothers living in more enclave-like neighborhoods were also more likely to have a public source of payment for their prenatal care, higher parity, and were less likely to smoke during pregnancy. The fathers of Hispanic children living in more enclave-like neighborhoods were more likely to have lower education, be Hispanic, and be slightly younger. Generally, more enclave-like neighborhoods were of disproportionately lower SES and predominantly located in Los Angeles County. Most of our study population lived in urban neighborhoods (Table 3.1).

Among Hispanic mothers living in the least enclave-like neighborhoods, we observed an increased risk of rhabdomyosarcoma [OR=1.57, 95% CI: (1.03, 2.38)] in the offspring compared with those living in the most enclave-like neighborhoods. However, we estimated decreases in

risk for AML [OR=0.73, 95% CI: (0.53, 1.03)], and retinoblastoma [OR=0.71, 95% CI: (0.50, 1.01)], particularly bilateral [OR=0.40, 95% CI: (0.20, 0.84)] in low enclave neighborhoods (Table 3.2).

When we stratified by maternal nativity status (Tables 3.3 and 3.4), the risk of AML and rhabdomyosarcoma in the least enclave-like neighborhoods were similar for offspring of US-born Hispanic mothers and foreign-born Hispanic mothers. In contrast, retinoblastoma showed a decreased risk among the offspring of foreign-born Hispanic mothers living in the least enclave-like neighborhoods [OR=0.52, 95% CI: (0.33, 0.83)] but estimates were largely null among US-born Hispanic mothers. Additionally, a decreased risk of hepatoblastoma was found only among the children of US-born Hispanic mothers in the least enclave-like neighborhoods compared with those in the most enclave-like neighborhoods [OR=0.41, 95% CI: (0.17, 0.98)].

When assessing the effect of Hispanic enclaves on childhood cancer risk in children born to Hispanic mothers starting in 1998 Table A 3.2), we found that estimates were similar to those that we observed in the entire sample, but with wider confidence intervals, with the exception of astrocytoma, which showed an increased risk [OR=1.44, 95% CI: (0.96, 2.17)] in the least enclave-like neighborhoods. In models additionally adjusted for traffic-related air pollution during the child's first year (Table A 3.3), the same overall pattern for cancer risk was seen with an even more highly elevated risk of astrocytoma in the least enclave-like neighborhoods [OR=1.75, 95% CI: (1.04, 2.96)]. We checked the estimates for astrocytoma in the period 1998-2007 to ensure that the increase OR was not due to the exclusion of years by assessing the effect of living in the least enclave-like neighborhoods, adjusting for all factors except CO, in this subgroup and found that the drop in years did not account for this increase ([OR=1.05, 95% CI: 0.72, 1.52)].

In sensitivity analyses, we examined the individual factors that contributed to the index, and found that overall patterns were similar to the entire sample with a few notable exceptions. For AML, we observed a null association in neighborhoods with a low percent of Hispanics [Adjusted OR=1.11, 95% CI: (0.79, 1.58)]. For hepatoblastoma, a decreased risk was apparent in neighborhoods with a low percent of Hispanics [Adjusted OR=0.59, 95% CI: 0.36, 0.95], and when stratified further by nativity, this decreased risk was seen in both foreign- and US-born mothers [Adjusted OR=0.62, 95% CI: 0.34, 1.12; Adjusted OR=0.53, 95% CI: 0.23, 1.21, respectively]. For rhabdomyosarcoma, we did not observe an increased risk with a low proportion of Hispanics and limited English proficiency, but when examining this further, this was largely due to null associations among foreign-born mothers [Adjusted OR=1.02, 95% CI: 0.64, 1.64; Adjusted OR=1.07, 95% CI: (0.69, 1.68)], respectively. We also observed an elevated risk of intracranial and intraspinal embryonal brain tumors and medulloblastoma in neighborhoods with a low proportion of recent immigrants [OR=1.36, 95% CI: 0.99, 1.88); OR=2.03, 95% CI: (1.03, 4.00), respectively] (data not shown).

When assessing associations separately for LA County and the Central Valley region, we found similar associations as reported for the entire population, except for an elevated risk of ALL and Wilms in low-enclave-like neighborhoods in LA county [OR=1.39, 95% CI: (1.00, 1.93), OR=1.82, 95% CI: (1.05, 3.16), respectively] [Table A 3.4]. When examining associations between residence in enclaves for Hispanic mothers and childhood cancers in urban tracts only we found similar associations as in our entire study population, except for a slightly elevated risk of Wilms tumor in low enclave-like neighborhoods [OR=1.29, 95% CI: (0.96, 1.72)] [Table A 3.5].

Associations between enclave residence and cancers among offspring of Mexican mothers only were similar to those reported for foreign-born mothers, except for a marked attenuation in risk of rhabdomyosarcoma in low enclave-like neighborhoods [OR=95% CI: 1.23 (0.64, 2.36)] [Table A 3.6].

3.5 Discussion

In this population-based sample of children born to Hispanic mothers in California, we did not find a uniformly beneficial effect of enclaves on offspring health in terms of childhood cancers. We found a decreased risk of retinoblastoma, particularly for offspring of foreign-born mothers, living in the least enclave-like neighborhoods. Hepatoblastoma risk was also reduced in the least enclave-like neighborhoods, particularly for US-born Hispanic mothers. For AML, we found a decreased risk in the least enclave-like neighborhoods and associations did not vary substantially by maternal nativity, but were most pronounced for immigration-related factors (ie. low % of foreign born, linguistic isolation, limited English proficiency, recent immigrants). In contrast, rhabdomyosarcoma risk was elevated in the least enclave-like neighborhoods.

Given our previous findings on childhood cancer risk among Hispanics by maternal birthplace, we expected that the risk of CNS tumors, neuroblastoma, and Wilms' tumor would be highest in the least enclave-like neighborhoods since risk for these tumors were found to be reduced for children of Hispanic mothers, particularly foreign-born mothers, compared with children of non-Hispanic white mothers [7]. Although we observed an increased risk of astrocytoma in low enclave-like neighborhoods in the 1998+ born subgroup and of intracranial and intraspinal brain tumors and medulloblastoma in neighborhoods with a low proportion of recent immigrants, we did not find a consistently increased risk of CNS tumors in low enclave-like neighborhoods. For neuroblastoma and Wilms' tumor we did not find any associations,

except for an elevated risk of Wilms' tumor in the least enclave-like neighborhoods in LA County and urban tracts.

Although Hispanic enclaves have been thought to offer positive health benefits, US-born mothers may benefit more from living in these enclaves than foreign-born mothers. Foreign-born Hispanic mothers who already have healthy behaviors may be sufficiently protected regardless of where they live whereas for US-born Hispanic mothers living in these enclaves may matter more in terms of cultural enforcement of healthy lifestyle norms [74]. For smoking during pregnancy, high enclave-like neighborhoods have been thought to offer positive health benefits due to the lower rates of smoking among foreign-born Hispanic mothers [74]. There is evidence that living in Hispanic enclaves decreases maternal smoking rates during pregnancy among Hispanic mothers, and a study that stratified by nativity found this to be exclusive to US-born Hispanics [74, 144, 145]. Because maternal smoking was only collected for part of our study period (2007+), we were not able to adjust for it. The strongest evidence for smoking during pregnancy on cancer risk has been reported for hepatoblastoma and retinoblastoma, but we did not find an increased risk of these cancers in the least-enclave like neighborhoods. However, other studies including our own from this population have shown strong evidence of an increased risk of CNS tumors with smoking during pregnancy as well, which may explain the increased risk of some CNS tumor types in low enclave-like neighborhoods [138, 146–150].

Though the most enclave-like neighborhoods have been found to lower the prevalence of pregnancy smoking, they may have higher prevalence of other negative prenatal factors (eg. lack of important nutrients in the maternal diet, exposure to harmful environmental agents, or exposure to occupational hazards), which could explain the comparatively lower risk of certain cancers in the least enclave-like neighborhoods. These factors may impact risk through cultural

and social norms and/or through access to health-promoting resources in neighborhoods. The risk of retinoblastoma and hepatoblastoma have been shown to decrease with greater consumption of healthy fruits and vegetables during pregnancy and with multivitamin use [64, 151]. Although no studies have looked at vitamin use in relation to enclaves, one study found lower consumption of fruits among Mexican Americans living in Mexican enclaves [152]. Another study found an elevated risk of gestational diabetes in Mexican enclaves in New York City among Mexican women [83]. There is strong evidence that hepatoblastoma is positively associated with low birthweight [110]. A study in LA found that working conditions in various jobs held mainly by first-generation immigrant Latina women increased the risk of term low birth weight [154]. Previous studies that examined Hispanic enclaves in relation to low birthweight among Hispanic women found that residing in an enclave was associated with no risk [74, 155] or a higher risk of low birthweight [156]. Studies that differentiated by nativity status found no associations with low birthweight among foreign-born Hispanic mothers, but a decreased risk of low birthweight among US-born Hispanic mothers [157, 158]. Thus, the literature to date is inconclusive with respect to the effects of these enclaves on birthweight. Since the association for retinoblastoma was particularly strong for bilateral disease, which has been shown to be most related to paternal preconception exposures, paternal exposures may be of particular interest [159]. Paternal occupational exposures to non-welding metals and pesticides as well as an unhealthy diet have been shown to increase the risk of bilateral retinoblastoma [160, 161].

Most patterns in cancer risk were fairly consistent when assessing the individual factors contributing to the index, except for AML, which was not inversely associated with a low percent of Hispanics in a neighborhood. AML did not vary much by maternal nativity status.

Prenatal factors that are suggestive of an increased risk for AML include older maternal age, increasing birth order, prior fetal loss, maternal alcohol use, and maternal exposure to pesticides [162]. However, even after adjustment for maternal age, birth order, and prior fetal loss, the associations we observed with AML persisted. We lacked data on maternal alcohol use and exposure to pesticides thus confounding by these factors is possible.

There are few known environmental risk factors for childhood cancers. Studies have shown that air pollutants are associated with increased risk of certain childhood cancers [143, 163, 164] and that high enclave-like neighborhoods have higher traffic exposure [165, 166]. However, when we controlled for traffic-related air pollution, the effect estimates we observed persisted, suggesting that air pollution did not account for the differences we saw by enclave status, though the possibility of residual confounding by air pollution remains. Given the potential link between exposure to pesticides and AML, in sensitivity analyses we restricted to Los Angeles County and the Central Valley counties, and examined exclusion of enclaves located in rural agricultural areas. The patterns we reported on did not change except for ALL and Wilms' tumor. ALL was elevated in low-enclave-like neighborhoods in LA County while Wilms' tumor was elevated in low enclave-like neighborhoods in LA County and in urban only tracts. The risk of ALL has been shown to be increased in highly urbanized areas and near toxic sites in various studies [167, 168] . One study found this even after controlling for traffic-related air pollution and benzene. They suggested that this may be explained by the lower likelihood of exposure to infections due to the more hygienic conditions in these environments that in turn could later lead to overstimulation of the immune response [168]. This is plausible as exposure to infections in early life have been shown to be associated with a decreased risk of ALL [169]. Given that the Hispanic population in Los Angeles has one of the highest childhood cancer rates

worldwide, further investigation of environmental factors that may be prevalent in these neighborhoods would be of interest [132]. Our numbers were small when conducting these sub-group analyses, thus some results may be chance findings, especially since the increased risk of ALL was only apparent after adjustment for SES.

Rhabdomyosarcoma was the only cancer which we consistently found elevated in low-enclave like neighborhoods, and this effect seemed to be most pronounced for US- and foreign-born mothers from countries other than Mexico. We were unable to ascertain which countries these foreign-born mothers were predominantly from as country of birth prior to 2009 was only collected in the following manner: Puerto Rico, the Virgin Islands, Guam, Mexico, China, Japan, the Philippines, Vietnam, Canada, Cuba, or the rest of the world. Of the studies that have examined perinatal factors in relation to rhabdomyosarcoma, few potential risk factors have been suggested, including parental drug use, prenatal exposure to x-rays, birth control use, anemia during pregnancy, abnormal vaginal bleeding during pregnancy, high and low birthweight, and preterm birth [170]. We previously found an increased risk of rhabdomyosarcoma with late or no prenatal care [171], but after adjustment for this variable our enclave results were unchanged. Another potential explanation for the increased risk of rhabdomyosarcoma in these neighborhoods is the inverse association for rhabdomyosarcoma that has been found for atopic exposures (ie. breastfeeding, day care attendance, allergies, hives), suggesting that this cancer may share risk factors with ALL [172]. Indeed, studies have found that Hispanics residing in immigrant enclaves have a lower prevalence of asthma and respiratory conditions [173, 174]. Additionally, our finding for rhabdomyosarcoma may be due to chance as it was not consistent across our sensitivity analyses.

This study was limited by the lack of detailed covariate information on parental characteristics and exposures. Thus, confounding by known risk factors (smoking during pregnancy) and unknown risk factors is possible. Furthermore, we did not have information to determine whether differences exist among foreign-born Hispanics based on duration of residence in the US, as well as among US-born Hispanics by degree of acculturation.

There is also potential for misclassification of exposure as residence was ascertained using zip codes prior to 1998. However, when we examined the effect of enclaves in the subgroup with full residential address (1998+), most estimates were consistent with our results for the entire sample. In addition, we relied on address at birth, which may also be a source of misclassification if mothers moved during pregnancy. A review found that 9–32% of women in the United States and abroad, in studies from the 1980s–2000s, move residence during pregnancy, although most moves are local (median distance, <10 km) [175]. Since our neighborhood-level information was based on US census data, which was not available on a yearly basis, we relied on the assumption that neighborhoods remained stable in the span of 5 to 10 years. The definition of a neighborhood is also subjective and census boundaries may not accurately reflect the neighborhood of an individual, but census tracts are commonly used neighborhood boundaries and considered to be homogenous with respect to various sociodemographic characteristics [85]. Additionally, there is the potential for confounding by self-selection, whereby those with certain risk factors for childhood cancers may be more likely to choose to reside in these enclaves.

In spite of these various limitations, this study was the first to assess the effect of Hispanic enclaves in relation to childhood cancer risk. The neighborhood environment may be a determinant of cancer risk and may contribute to disparities in cancer outcomes and allow for

targeted studies and interventions. The population-based design also allowed for a comprehensive assessment of childhood cancer types.

In conclusion, overall we found that residence in Hispanic enclaves did not have a uniformly beneficial effect on childhood cancer. We were not able to confirm a consistently increased risk of the childhood cancers we hypothesized to be most related to health behaviors (CNS tumors, neuroblastoma, and Wilms' tumor) based on our previous findings [7]. There was substantial variation in our results depending on the nativity status of the mother and the region of residence within California. This suggests that Hispanic enclaves in themselves may not be a useful predictor of risk, rather further investigations into perinatal risk and preventive factors within Hispanic enclaves by maternal nativity and regions in California are needed in order to better understand the patterns in cancer risk we observed.

3.6 Tables

Table 3.1 Distribution of individual and neighborhood level characteristics among children of Hispanic mothers by Hispanic enclave tertile, birth years 1983-2011			
	Hispanic Enclave Index		
	N (%)		
	1 (low)	2 (intermediate)	3 (high)
Maternal education, y[a]			
8 or less	5869 (16.3)	6531 (21.8)	15606 (29.6)
9-11	8105 (22.5)	8209 (27.4)	16620 (31.5)
12	11036 (30.6)	8851 (29.5)	13291 (25.2)
13-15	6828 (18.9)	4345 (14.5)	5148 (9.8)
16 or more	3730 (10.3)	1615 (5.4)	1485 (2.8)
Missing	542 (1.5)	445 (1.5)	660 (1.3)
Maternal race			
White	38007 (96.7)	31712 (97.7)	57861 (98.5)
Black	203 (0.5)	137 (0.4)	116 (0.2)
Asian/Pacific Islander	878 (2.2)	534 (1.6)	690 (1.2)
Native American	182 (0.5)	77 (0.2)	83 (0.1)
Missing	18 (0.1)	9 (0.0)	6 (0.0)
Maternal age, y			
<20	5254 (13.4)	4522 (13.9)	8823 (15.0)
20-29	21608 (55.0)	18716 (57.6)	33908 (57.7)
30-34	8028 (20.4)	5910 (18.2)	10292 (17.5)
35+	4394 (11.2)	3318 (10.2)	5720 (9.7)
Missing	4 (0.0)	3 (0.0)	13 (0.0)
Source of payment for prenatal care[a]			
Private	15421 (42.7)	9898 (33.0)	12317 (23.3)
Public (Medi-Cal) or self-pay	20118 (55.7)	19775 (65.9)	39857 (75.5)
Missing	571 (1.6)	323 (1.1)	636 (1.2)
Maternal Nativity			
Foreign-born	20574 (52.4)	20368 (62.7)	43575 (74.2)
US-born	18698 (47.6)	12087 (37.2)	15161 (25.8)
Missing	16 (0.0)	14 (0.0)	20 (0.0)
Parity			
0	14551 (37.0)	11351 (35.0)	19928 (33.9)
1	11908 (30.3)	9563 (29.5)	17047 (29.0)
2 or more	12815 (32.6)	11541 (35.5)	21770 (37.1)
Missing	14 (0.0)	14 (0.0)	11 (0.0)
Multiple births			
Single	38443 (97.9)	31809 (98.0)	57672 (98.2)
Multiple	845 (2.2)	660 (2.0)	1084 (1.8)
Prenatal care initiation			
First trimester	29579 (75.3)	24637 (75.9)	43471 (74.0)
After first trimester or no care	9195 (23.4)	7297 (22.5)	14327 (24.4)
Missing	514 (1.3)	535 (1.7)	958 (1.6)
Smoking during pregnancy[b]			
Yes	105 (1.5)	49 (0.8)	45 (0.5)
No	6924 (97.0)	5793 (97.9)	8791 (96.9)
Missing	112 (1.6)	76 (1.3)	237 (2.6)
Birthweight, g			
Low birthweight (<2500)	2057 (5.2)	1759 (5.4)	3109 (5.3)
Normal birthweight (2500-<4000)	33236 (84.6)	27373 (84.3)	49802 (84.8)

High birthweight (4000+)	3971 (10.1)	3312 (10.2)	5799 (9.9)
Missing	24 (0.1)	25 (0.1)	46 (0.1)
Paternal education, y[a]			
8 or less	6134 (17.0)	6663 (22.2)	15349 (29.1)
9-11	6602 (18.3)	6769 (22.6)	13608 (25.8)
12	10774 (29.8)	8796 (29.3)	12759 (24.2)
13-15	5640 (15.6)	3411 (11.4)	4024 (7.6)
16 or more	3973 (11.0)	3411 (11.4)	1501 (2.8)
Missing	2987 (8.3)	2783 (9.3)	5569 (10.6)
Paternal ethnicity			
Hispanic	29390 (74.8)	27970 (86.1)	53466 (91.0)
Non-Hispanic	7972 (20.3)	2813 (8.7)	2090 (3.6)
Missing	1926 (4.9)	1686 (5.2)	3200 (5.5)
Paternal age, y			
<20	1937 (4.9)	1711 (5.3)	3048 (5.2)
20-29	18582 (47.3)	16036 (49.4)	29519 (50.2)
30-34	8553 (21.8)	6662 (20.5)	11625 (19.8)
35+	7652 (19.5)	5697 (17.6)	9548 (16.3)
Missing	2564 (6.5)	2363 (7.3)	5016 (8.5)
Neighborhood SES			
1 (low)	3214 (8.2)	9864 (30.4)	40898 (69.6)
2	11226 (28.6)	11704 (36.1)	14279 (24.3)
3	10138 (25.8)	8128 (25.0)	2756 (4.7)
4	9421 (24.0)	2178 (6.7)	646 (1.1)
5 (high)	5256 (13.4)	578 (1.8)	60 (0.1)
Missing	33 (0.1)	17 (0.1)	117 (0.2)
Urban			
Yes	35783 (91.1)	30234 (93.1)	55793 (94.9)
No	3505 (8.9)	2235 (6.9)	3017 (5.1)
Regions in CA			
Los Angeles County	6537 (16.6)	11598 (35.7)	32393 (55.1)
Central Valley	11075 (28.2)	5635 (17.4)	5947 (10.1)
Other	21676 (55.2)	15236 (46.9)	20416 (34.8)

[a]collected 1989+
[b]collected 2007+

Table 3.2 Adjusted ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertile									
	Hispanic Enclave Index								
	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]
	1 (low)			2 (intermediate)			3 (high)		
Controls	37464	1.00	1.00	30927	1.00	1.00	56010	1.00	1.00
Cases	1824	0.99	0.94 (0.86, 1.03)	1542	1.02	0.96 (0.89, 1.03)	2746	ref	ref
Leukemia	750	0.98	0.96 (0.83, 1.06)	613	0.97	0.94 (0.84, 1.06)	1161	ref	ref
---ALL	621	1.00	0.99 (0.85, 1.15)	495	0.98	0.94 (0.83, 1.07)	944	ref	ref
---AML	95	0.84	0.73 (0.52, 1.03)	83	0.87	0.87 (0.65, 1.17)	168	ref	ref
Astrocytoma	106	1.08	1.04 (0.72, 1.49)	87	1.08	0.99 (0.72, 1.35)	147	ref	ref
Ependymoma	38	1.10	0.86 (0.49, 1.51)	32	1.11	0.96 (0.58, 1.57)	51	ref	ref
Intracranial	93	1.11	1.18 (0.86, 1.62)	85	1.24	1.25 (0.94, 1.66)	126	ref	ref
---PNET	35	0.83	0.90 (0.54, 1.49)	38	1.13	1.14 (0.75, 1.74)	65	ref	ref
---Medulloblastoma	37	1.29	1.48 (0.87, 2.55)	30	1.26	1.28 (0.76, 2.15)	43	ref	ref
Germ cell	58	0.98	0.90 (0.59, 1.36)	48	0.98	0.94 (0.65, 1.37)	88	ref	ref
---Yolk sac tumors	26	0.92	0.90 (0.53, 1.54)	18	0.77	0.71 (0.40, 1.26)	42	ref	ref
---Teratoma	28	1.15	0.87 (0.46, 1.62)	28	1.39	1.30 (0.73, 2.31)	36	ref	ref
Hepatoblastoma	51	1.01	0.87 (0.54, 1.42)	47	1.12	1.05 (0.70, 2.58)	74	ref	ref
NHL	34	0.79	0.73 (0.39, 2.37)	43	1.23	1.18 (0.71, 1.97)	65	ref	ref
Neuroblastoma	159	1.19	0.87 (0.65, 1.16)	127	1.15	0.95 (0.74, 1.21)	198	ref	ref
Retinoblastoma	94	0.91	0.71 (0.50, 1.01)	101	1.17	1.05 (0.79, 1.40)	154	ref	ref
---Unilateral	73	1.05	0.87 (0.58, 1.30)	63	1.10	1.03 (0.72, 1.48)	104	ref	ref
---Bilateral	20	0.61	0.40 (0.20, 0.84)	37	1.36	1.08 (0.66, 1.76)	48	ref	ref
Soft tissue sarcomas	101	1.35	1.28 (0.92, 1.77)	70	1.20	0.99 (0.72, 1.35)	134	ref	ref
---Rhabdomyosarcoma	68	1.38	1.57 (1.03, 2.38)	50	1.41	1.28 (0.86, 1.91)	75	ref	ref
Wilms' tumor	145	1.22	1.11 (0.84, 1.47)	114	1.17	1.01 (0.77, 1.31)	178	ref	ref

[a]adjusted for year of birth

[b]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[c]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table 3.3 Adjusted ORs for childhood cancer risk among children of foreign-born Hispanic mothers by Hispanic enclave tertile									
	Hispanic Enclave Index								
	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]
	1 (low)			2 (intermediate)			3 (high)		
Controls	19689	1.00	1.00	19428	1.00	1.00	41604	1.00	1.00
Cases	885	0.95	0.93 (0.83, 1.04)	940	1.02	0.99 (0.90, 1.08)	1971	ref	ref
Leukemia	369	0.92	0.92 (0.79, 1.08)	384	0.98	0.97 (0.85, 1.11)	855	ref	ref
---ALL	298	0.91	0.92 (0.77, 1.11)	313	0.98	0.98 (0.84, 1.14)	702	ref	ref
---AML	49	0.87	0.79 (0.51, 1.22)	47	0.84	0.81 (0.56, 1.17)	118	ref	ref
Astrocytoma	41	0.86	0.77 (0.48, 1.21)	55	1.17	1.04 (0.73, 1.48)	101	ref	ref
Ependymoma	14	0.86	0.60 (0.26, 1.41)	15	0.92	0.71 (0.37, 1.39)	34	ref	ref
Intracranial	39	0.91	1.04 (0.66, 1.66)	57	1.38	1.52 (1.06, 2.16)	91	ref	ref
---PNET	16	0.68	0.79 (0.38, 1.62)	22	1.00	1.09 (0.64, 1.85)	51	ref	ref
---Medulloblastoma	15	1.17	1.39 (0.62, 3.11)	25	1.98	2.19 (1.20, 3.98)	27	ref	ref
Germ cell	33	1.04	0.95 (0.57, 1.58)	32	1.01	0.99 (0.63, 1.53)	67	ref	ref
---Yolk sac tumors	15	0.86	0.82 (0.44, 1.51)	11	0.63	0.64 (0.33, 1.23)	37	ref	ref
---Teratoma	15	1.31	0.94 (0.41, 2.15)	19	1.66	1.46 (0.72, 2.96)	24	ref	ref
Hepatoblastoma	32	1.43	1.31 (0.77, 2.24)	32	1.42	1.39 (0.86, 2.24)	47	ref	ref
NHL	18	0.62	0.82 (0.39, 1.72)	28	0.91	1.38 (0.74, 1.72)	44	ref	ref
Neuroblastoma	84	1.36	1.03 (0.71, 1.50)	64	1.04	0.84 (0.60, 1.19)	130	ref	ref
Retinoblastoma	41	0.73	0.52 (0.33, 0.83)	58	1.04	0.98 (0.68, 1.42)	118	ref	ref
---Unilateral	30	0.84	0.62 (0.36, 1.08)	35	0.99	1.00 (0.62, 1.61)	76	ref	ref
---Bilateral	11	0.58	0.39 (0.17, 0.88)	22	1.15	0.92 (0.51, 1.66)	40	ref	ref
Soft tissue sarcomas	47	1.00	1.27 (0.80, 2.00)	44	0.95	0.98 (0.66, 1.46)	99	ref	ref
---Rhabdomyosarcoma	32	1.25	1.55 (0.88, 2.76)	36	1.42	1.47 (0.91, 2.39)	54	ref	ref
Wilms' tumor	71	1.20	1.26 (0.85, 1.85)	69	1.19	1.09 (0.79, 1.50)	126	ref	ref

[a]adjusted for year of birth

[b]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[c]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table 3.4 Adjusted ORs for childhood cancer risk among children of US-born Hispanic mothers by Hispanic enclave tertile									
	Hispanic Enclave Index								
	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]
	1 (low)			2 (intermediate)			3 (high)		
Controls	17759	1.00	1.00	11486	1.00	1.00	14387	1.00	1.00
Cases	939	0.98	0.94 (0.83, 1.07)	601	0.97	0.92 (0.81, 1.04)	774	ref	ref
Leukemia	381	1.02	1.00 (0.81, 1.24)	228	0.94	0.91 (0.75, 1.10)	306	ref	ref
---ALL	323	1.09	1.09 (0.86, 1.38)	181	0.95	0.90 (0.72, 1.12)	242	ref	ref
---AML	46	0.74	0.70 (0.40, 1.21)	36	0.89	0.98 (0.61, 1.58)	50	ref	ref
Astrocytoma	65	1.15	1.53 (0.88, 2.64)	32	0.88	0.92 (0.53, 1.59)	46	ref	ref
Ependymoma	24	1.14	1.31 (0.59, 2.93)	17	1.24	1.44 (0.66, 3.15)	17	ref	ref
Intracranial	54	1.25	1.21 (0.74, 2.01)	28	1.00	0.94 (0.56, 1.57)	35	ref	ref
---PNET	19	1.11	1.21 (0.56, 2.61)	16	1.46	1.51 (0.69, 3.33)	14	ref	ref
---Medulloblastoma	22	1.11	1.17 (0.55, 2.49)	5	0.39	0.39 (0.15, 1.04)	16	ref	ref
Germ cell	25	0.96	0.81 (0.39, 1.67)	16	0.95	0.87 (0.41, 1.86)	21	ref	ref
---Yolk sac tumors	11	1.77	1.37 (0.39, 4.86)	7	1.74	1.18 (0.32, 4.42)	5	ref	ref
---Teratoma	13	1.01	0.77 (0.29, 2.04)	9	1.12	1.05 (0.39, 2.78)	12	ref	ref
Hepatoblastoma	19	0.56	0.41 (0.17, 0.98)	15	0.68	0.58 (0.27, 1.25)	27	ref	ref
NHL	16	0.87	0.59 (0.19, 1.67)	15	1.40	0.80 (0.36, 1.76)	21	ref	ref
Neuroblastoma	75	0.89	0.71 (0.46, 1.10)	63	1.16	1.04 (0.71, 1.52)	68	ref	ref
Retinoblastoma	53	1.19	0.99 (0.56, 1.75)	43	1.48	1.20 (0.73, 1.99)	36	ref	ref
---Unilateral	43	1.24	1.15 (0.63, 2.11)	28	1.25	1.08 (0.60, 1.93)	28	ref	ref
---Bilateral	9	0.90	0.48 (0.12, 1.95)	15	2.29	1.54 (0.54, 4.39)	8	ref	ref
Soft tissue sarcomas	54	1.25	1.33 (0.79, 2.23)	26	0.93	1.00 (0.59, 1.680	35	ref	ref
---Rhabdomyosarcoma	36	1.39	1.57 (0.82, 3.01)	14	0.83	0.94 (0.47, 1.88)	21	ref	ref
Wilms' tumor	74	1.18	0.91 (0.59, 1.42)	45	1.10	0.90 (0.57, 1.42)	51	ref	ref

[a]adjusted for year of birth

[b]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[c]slight overcorrection for clustering in census tracts due to changes in tracts across years

3.7 Appendix

Table A 3.1 Adjusted ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertile using population averaged model

	Hispanic Enclave Index					
	N	Adjusted OR (95% CI)[a,b]	N	Adjusted OR (95% CI)[a,b]	N	Adjusted OR (95% CI)[a,b]
	1 (low)		2 (intermediate)		3 (high)	
Controls	37464	1.00	30927	1.00	56010	1.00
Cases	1824	0.95 (0.87, 1.03)	1542	0.96 (0.90, 1.04)	2746	ref
Leukemia	750	0.97 (0.85, 1.11)	613	0.95 (0.84, 1.06)	1161	ref
---ALL	621	1.00 (0.86, 1.16)	495	0.94 (0.83, 1.07)	944	ref
---AML	95	0.73 (0.52, 1.01)	83	0.87 (0.65, 1.17)	168	ref
Astrocytoma	106	1.08 (0.76, 1.53)	87	1.00 (0.73, 1.37)	147	ref
Ependymoma	38	0.68 (0.34, 1.36)	32	0.92 (0.56, 1.53)	51	ref
Glioma	164	1.01 (0.76, 1.32)	141	0.98 (0.77, 1.25)	248	ref
Intracranial	93	1.16 (0.86, 1.56)	85	1.25 (0.94, 1.66)	126	ref
---PNET	35	NE	38	NE	65	ref
---Medulloblastoma	37	1.47 (0.85, 2.53)	30	1.28 (0.75, 2.15)	43	ref
Germ cell	58	NE	48	NE	88	ref
---Yolk sac tumors	26	0.90 (0.55, 1.46)	18	0.71 (0.40, 1.25)	42	ref
---Teratoma	28	0.86 (0.46, 1.62)	28	1.30 (0.73, 2.30)	36	ref
Hepatoblastoma	51	0.88 (0.55, 1.42)	47	1.05 (0.70, 1.58)	74	ref
NHL	46	0.59 (0.36, 0.98)	42	0.71 (0.48, 1.05)	101	ref
Neuroblastoma	159	0.82 (0.62, 1.09)	127	0.94 (0.73, 1.20)	198	ref
Retinoblastoma	94	0.72 (0.50, 1.01)	101	1.05 (0.79, 1.40)	154	ref
---Unilateral	73	0.85 (0.58, 1.28)	63	1.03 (0.72, 1.48)	104	ref
---Bilateral	20	0.42 (0.20, 0.86)	37	1.08 (0.66, 1.76)	48	ref
Soft tissue sarcomas	101	1.29 (0.93, 1.80)	70	0.99 (0.73, 1.36)	134	ref
---Rhabdomyosarcoma	68	1.58 (1.04, 2.40)	50	1.29 (0.86, 1.91)	75	ref
Wilms' tumor	145	1.10 (0.83, 1.46)	114	1.01 (0.77, 1.31)	178	ref

[a]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age
NE=not estimable, model failed to converge
[b]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table A 3.2 Adjusted ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertile, birth years 1998-2011						
	N	Adjusted OR (95% CI)[a,b]	N	Adjusted OR (95% CI)[a,b]	N	Adjusted OR (95% CI)[a,b]
		1 (low)		2 (intermediate)		3 (high)
Controls	21436	1.00	18987	1.00	31510	1.00
Cases	1085	0.92 (0.82, 1.03)	936	0.94 (0.86, 1.03)	1567	ref
Leukemia	411	0.96 (0.80, 1.15)	356	0.96 (0.83, 1.12)	596	ref
---ALL	330	1.00 (0.82, 1.22)	274	0.95 (0.80, 1.12)	466	ref
---AML	60	0.78 (0.50, 1.21)	56	0.93 (0.65, 1.34)	102	ref
Astrocytoma	71	1.44 (0.96, 2.17)	55	1.19 (0.80, 1.77)	73	ref
Ependymoma	26	0.99 (0.52, 1.91)	23	1.02 (0.57, 1.82)	35	ref
Glioma	108	1.18 (0.85, 1.64)	95	1.11 (0.83, 1.49)	138	ref
Intracranial	55	1.08 (0.68, 1.73)	50	1.21 (0.81, 1.79)	63	ref
---PNET	15	0.78 (0.33, 1.87)	15	1.14 (0.58, 2.25)	20	ref
---Medulloblastoma	21	1.01 (0.51, 2.01)	21	1.05 (0.56, 1.98)	29	ref
Germ cell	28	0.72 (0.41, 1.26)	32	0.99 (0.62, 1.56)	51	ref
---Yolk sac tumors	11	0.63 (0.30, 1.34)	13	0.83 (0.41, 1.65)	25	ref
---Teratoma	16	0.82 (0.34, 1.98)	17	1.18 (0.59, 2.37)	21	ref
Hepatoblastoma	34	0.84 (0.44, 1.57)	27	0.88 (0.51, 1.52)	51	ref
NHL	23	0.50 (0.25, 1.01)	22	0.61 (0.36, 1.02)	57	ref
Neuroblastoma	91	0.80 (0.55, 1.16)	75	0.84 (0.61, 1.16)	129	ref
Retinoblastoma	55	0.68 (0.44, 1.06)	62	0.99 (0.69, 1.43)	91	ref
---Unilateral	41	0.80 (0.47, 1.36)	35	0.88 (0.56, 1.41)	62	ref
---Bilateral	13	0.42 (0.17, 1.02)	26	1.18 (0.63, 2.23)	27	ref
Soft tissue sarcomas	64	1.33 (0.87, 2.05)	40	0.96 (0.64, 1.44)	78	ref
---Rhabdomyosarcoma	44	1.71 (0.99, 2.94)	30	1.37 (0.83, 2.25)	43	ref
Wilms' tumor	89	1.04 (0.69, 1.55)	58	0.85 (0.59, 1.21)	95	ref

[a]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[b]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table A 3.3 ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertile adjusted for traffic-related air pollution in child's first year, birth years 1998-2007			
	1 (low)	2 (intermediate)	3 (high)
	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]
Cases	0.89 (0.77, 1.03)	0.93 (0.83, 1.06)	ref
Leukemia	0.79 (0.64, 0.99)	0.88 (0.73, 1.06)	ref
---ALL	0.80 (0.62, 1.03)	0.87 (0.70, 1.07)	ref
---AML	0.61 (0.34, 1.09)	0.84 (0.52, 1.34)	ref
Astrocytoma	1.75 (1.04, 2.95)	1.35 (0.82, 2.19)	ref
Ependymoma	0.62 (0.25, 1.57)	0.62 (0.27, 1.40)	ref
Glioma	1.21 (0.78, 1.87)	1.07 (0.73, 1.58)	ref
Intracranial	1.44 (0.74, 2.79)	1.55 (0.94, 2.57)	ref
---PNET	1.13 (0.38, 3.38)	1.34 (0.57, 3.14)	ref
---Medulloblastoma	1.10 (0.41, 2.93)	1.45 (0.64, 3.30)	ref
Germ cell	0.82 (0.37, 1.81)	1.21 (0.68, 2.17)	ref
---Yolk sac tumors	0.72 (0.27, 1.94)	0.91 (0.37, 2.20)	ref
---Teratoma	0.97 (0.30, 3.08)	1.83 (0.85, 3.94)	ref
Hepatoblastoma	0.66 (0.27, 1.64)	1.05 (0.51, 2.17)	ref
NHL	0.54 (0.24, 1.22)	0.37 (0.18, 0.75)	ref
Neuroblastoma	0.85 (0.51, 1.42)	0.91 (0.59, 1.40)	ref
Retinoblastoma	0.58 (0.30, 1.09)	1.07 (0.68, 1.68)	ref
---Unilateral	0.82 (0.40, 1.70)	1.02 (0.59, 1.76)	ref
---Bilateral	0.27 (0.08, 0.99)	1.18 (0.55, 2.55)	ref
Soft tissue sarcomas	1.25 (0.69, 2.26)	0.88 (0.52, 1.49)	ref
---Rhabdomyosarcoma	1.54 (0.71, 3.53)	1.29 (0.69, 2.43)	ref
Wilms' tumor	1.04 (0.61, 1.78)	0.83 (0.52, 1.32)	ref

[a]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age, CO

[b]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table A 3.4 Adjusted ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertiles stratified by region in CA									
	Hispanic Enclave Index								
	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]	N	Crude OR[a]	Adjusted OR (95% CI)[b,c]
	1 (low)			2 (intermediate)			3 (high)		
Los Angeles County									
Controls	6209	1.00	1.00	11074	1.00	1.00	30823	1.00	1.00
Cases	328	1.04	1.05 (0.87, 1.27)	524	0.93	0.87 (0.77, 0.99)	1570	ref	ref
Leukemia	130	1.01	1.25 (0.93, 1.67)	204	0.88	0.86 (0.69, 1.06)	666	ref	ref
---ALL	105	1.00	1.39 (1.00, 1.93)	158	0.84	0.86 (0.67, 1.10)	547	ref	ref
---AML	19	1.05	0.73 (0.34, 1.54)	33	1.02	0.80 (0.49, 1.31)	89	ref	ref
Astrocytoma	9	0.56	0.51 (0.18, 1.44)	32	1.10	0.99 (0.54, 1.82)	83	ref	ref
Ependymoma	7	1.26	0.83 (0.32, 2.16)	12	1.22	0.91 (0.42, 1.97)	27	ref	ref
Intracranial	23	1.46	1.50 (0.80, 2.80)	37	1.32	1.34 (0.88, 2.04)	78	ref	ref
Germ cell	8	0.77	0.78 (0.32, 1.91)	13	0.70	0.74 (0.34, 1.61)	51	ref	ref
Hepatoblastoma	10	0.97	0.63 (0.21, 1.87)	18	1.00	0.88 (0.44, 1.78)	47	ref	ref
NHL	8	0.75	0.51 (0.19, 1.37)	17	0.89	0.74 (0.41, 1.32)	56	ref	ref
Neuroblastoma	32	1.43	0.94 (0.48, 1.84)	39	0.98	0.72 (0.46, 1.13)	110	ref	ref
Retinoblastoma	11	0.57	0.42 (0.18, 0.95)	41	1.21	1.22 (0.77, 1.95)	91	ref	ref
Soft tissue sarcomas	21	1.47	1.92 (0.94, 3.91)	26	1.01	1.06 (0.60, 1.86)	72	ref	ref
---Rhabdomyosarcoma	16	1.96	2.90 (1.37, 6.15)	19	1.30	1.37 (0.68, 2.75)	41	ref	ref
Wilms' tumor	30	1.53	1.82 (1.05, 3.16)	34	0.96	0.81 (0.51, 1.28)	101	ref	ref
Central Valley									
Controls	10589	1.00	1.00	5369	1.00	1.00	5674	1.00	1.00
Cases	486	0.95	0.84 (0.66, 1.08)	266	1.03	1.00 (0.84, 1.18)	273	ref	ref
Leukemia	204	0.85	0.77 (0.53, 1.12)	102	0.84	0.88 (0.66, 1.17)	129	ref	ref
---ALL	177	0.96	0.91 (0.61, 1.37)	80	0.88	0.94 (0.68, 1.29)	97	ref	ref
---AML	20	0.44	0.42 (0.17, 1.06)	16	0.63	0.68 (0.37, 1.25)	26	ref	ref
Astrocytoma	34	1.68	1.12 (0.30, 3.18)	17	1.62	1.41 (0.63, 3.14)	11	ref	ref
Ependymoma	10	1.12	0.64 (0.10, 3.96)	6	1.24	1.07 (0.31, 3.67)	5	ref	ref
Glioma	50	1.24	0.86 (0.39, 1.91)	30	1.43	1.15 (0.63, 2.07)	22	ref	ref
Intracranial	26	1.30	1.42 (0.62, 3.27)	11	1.21	1.10 (0.48, 2.55)	10	ref	ref

Germ cell	13	0.99	0.53 (0.18, 1.54)	7	1.06	0.88 (0.30, 2.61)	7	ref	ref
Hepatoblastoma	15	1.20	1.39 (0.36, 5.42)	9	1.33	1.42 (0.50, 4.05)	7	ref	ref
NHL	18	2.24	0.75 (0.52, 1.09)	7	1.93	0.80 (0.57, 1.12)	4	ref	ref
Neuroblastoma	36	0.77	0.53 (0.23, 1.20)	24	1.01	0.94 (0.52. 1.70)	25	ref	ref
Retinoblastoma	21	0.65	0.68 (0.22, 2.09)	16	1.01	0.94 (0.47, 1.87)	17	ref	ref
Soft tissue sarcomas	27	1.33	1.06 (0.37, 3.08)	13	1.24	1.23 (0.52, 2.87)	11	ref	ref
---Rhabdomyosarcoma	16	1.48	1.61 (0.44, 5.94)	10	1.73	1.94 (0.66, 5.72)	6	ref	ref
Wilms' tumor	38	1.30	1.09 (0.47, 2.53)	20	1.44	1.33 (0.68, 2.60)	15	ref	ref

[a]adjusted for year of birth

[b]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[c]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table A 3.5 Adjusted ORs for childhood cancer risk among children of Mexican mothers by Hispanic enclave tertile			
	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]
	1 (low)	2 (intermediate)	3 (high)
Cases	0.94 (0.82, 1.06)	0.98 (0.89, 1.08)	ref
Leukemia	0.92 (0.77, 1.09)	0.95 (0.82, 1.11)	ref
---ALL	0.91 (0.74, 1.11)	0.96 (0.81, 1.13)	ref
---AML	0.83 (0.53, 1.20)	0.80 (0.53, 1.20)	ref
Astrocytoma	0.78 (0.49, 1.25)	0.98 (0.67, 1.43)	ref
Ependymoma	0.56 (0.21, 1.48)	0.81 (0.41, 1.61)	ref
Intracranial	0.92 (0.55, 1.54)	1.42 (0.98, 2.08)	ref
---PNET	0.79 (0.38, 1.65)	1.05 (0.60, 1.83)	ref
---Medulloblastoma	1.26 (0.50, 3.18)	2.49 (1.27, 4.87)	ref
Germ cell	0.98 (0.58, 1.63)	0.95 (0.59, 1.52)	ref
---Yolk sac tumors	0.79 (0.42, 1.47)	0.65 (0.33, 1.25)	ref
---Teratoma	1.03 (0.43, 2.46)	1.37 (0.62, 3.03)	ref
Hepatoblastoma	1.42 (0.82, 2.43)	1.43 (0.87, 2.37)	ref
NHL	0.65 (0.34, 1.24)	0.73 (0.43, 1.25)	ref
Neuroblastoma	0.99 (0.67, 1.46)	0.78 (0.54, 1.13)	ref
Retinoblastoma	0.57 (0.35, 0.92)	0.97 (0.64, 1.47)	ref
---Unilateral	0.71 (0.38, 1.31)	1.12 (0.64, 1.94)	ref
---Bilateral	0.40 (0.17, 0.93)	0.80 (0.42, 1.50)	ref
Soft tissue sarcomas	1.06 (0.64, 1.73)	0.93 (0.61, 1.41)	ref
---Rhabdomyosarcoma	1.23 (0.64, 2.36)	1.52 (0.91, 2.53)	ref
Wilms' tumor	1.37 (0.89, 2.09)	1.18 (0.83, 1.67)	ref

[a]adjusted for year of birth, maternal age, census-based SES, paternal ethnicity, paternal age
[b]slight overcorrection for clustering in census tracts due to changes in tracts across years

Table A 3.6. Adjusted ORs for childhood cancer risk among children of Hispanic mothers by Hispanic enclave tertile in urban tracts			
	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]	Adjusted OR (95% CI)[a,b]
	1 (low)	2 (intermediate)	3 (high)
Cases	0.95 (0.87, 1.04)	0.96 (0.89, 1.03)	ref
Leukemia	0.95 (0.83, 1.09)	0.94 (0.83, 1.06)	ref
---ALL	0.98 (0.85, 1.14)	0.94 (0.82, 1.07)	ref
---AML	0.75 (0.52, 1.08)	0.89 (0.66, 1.20)	ref
Astrocytoma	0.98 (0.68, 1.40)	0.96 (0.69, 1.32)	ref
Ependymoma	0.78 (0.44, 1.40)	0.88 (0.53, 1.46)	ref
Intracranial	1.16 (0.82, 1.63)	1.21 (0.90, 1.62)	ref
---PNET	0.94 (0.55, 1.60)	1.11 (0.71, 1.74)	ref
---Medulloblastoma	1.28 (0.71, 2.31)	1.12 (0.65, 1.94)	ref
Germ cell	0.94 (0.62, 1.42)	1.04 (0.71, 1.53)	ref
---Yolk sac tumors	0.96 (0.54, 1.71)	0.81 (0.45, 1.45)	ref
---Teratoma	0.94 (0.49, 1.81)	1.41 (0.78, 2.53)	ref
Hepatoblastoma	0.95 (0.57, 1.56)	1.06 (0.70, 1.63)	ref
NHL	0.69 (0.41, 1.16)	0.73 (0.49, 1.09)	ref
Neuroblastoma	0.90 (0.67, 1.20)	0.91 (0.70, 1.17)	ref
Retinoblastoma	0.68 (0.47, 0.99)	1.00 (0.74, 1.35)	ref
---Unilateral	0.82 (0.54, 1.26)	1.02 (0.70, 1.48)	ref
---Bilateral	0.42 (0.20, 0.89)	0.94 (0.57, 1.54)	ref
Soft tissue sarcomas	1.23 (0.87, 1.73)	0.96 (0.69, 1.33)	ref
---Rhabdomyosarcoma	1.43 (0.92, 2.02)	1.27 (0.84, 1.92)	ref
Wilms' tumor	1.29 (0.96, 1.72)	1.05 (0.80, 1.38)	ref

[a]adjusted for year of birth, maternal age, maternal nativity, census-based SES, paternal ethnicity, paternal age

[b]slight overcorrection for clustering in census tracts due to changes in tracts across years

Chapter 4. Study 3: Prenatal air pollution exposure, smoking, and placental vascular resistance

4.1 Abstract

Background: Exposure to air pollution and smoking during pregnancy may impact placental vascular resistance, thereby increasing the risk of pregnancy complications and adverse birth outcomes. Few studies to date have examined air pollution in relation to placental vascular resistance and none of these examined whether smoking is also an independent risk factor for increased placental vascular resistance.

Methods: Our study included 566 pregnant women recruited between 1993 and 1996 in Los Angeles who completed 3 visits at 3 gestational ages. Detailed information on the pregnancy, including smoking, was collected and Doppler ultrasound was used to measure placental vascular resistance at each visit. Three placental vascular resistance indices were calculated: the resistance index, the pulsatility index, and the S/D ratio. We estimated exposure to NO_2 at the home address of the mother using a LUR model developed for LA county.

Results: NO_2 exposure increased the risk of high uterine artery resistance in late pregnancy (35-37 weeks). For smoking we found that being a former smoker increases umbilical resistance indices in the third exam while smoking during pregnancy increases the risk of higher umbilical and uterine resistance values, as well as uterine bilateral notching at the second exam.

Conclusions: We found that prenatal exposure to air pollution and smoking are associated with an increased risk of high placental vascular resistance. Our results suggest that further study of the mechanisms underlying this association as well as consideration of the impacts of smoking in air pollution and placental vascular resistance studies is warranted.

4.2 Introduction

Maternal exposure to air pollution during pregnancy has been linked to several adverse birth outcomes including low birth weight, and preterm and small for gestational age births [89]. Studies have also found an increased risk of gestational hypertension and preeclampsia with prenatal air pollution exposure [88]. Maternal hypertensive disorders and IUGR are hypothesized to share common pathways as they are both characterized by abnormal placenta formation and subsequent inadequate uteroplacental blood flow [176, 177]. Smoking during pregnancy has also been consistently associated with a number of adverse birth outcomes (fetal growth restriction, preterm birth, stillbirth) and pregnancy complications (placental abruption, placenta previa, spontaneous abortions, ectopic pregnancies) [96]. Interestingly, smoking has been found to reduce risk of preeclampsia, though the mechanisms for this are not well understood [96, 178]. Thus, further studies that aim to examine the impact of smoking on placental development and function are needed.

Doppler ultrasound has long been used to assess placental resistance to blood flow and to register the presence of ‘notching’ in uterine and umbilical arteries. In non-pregnant women and in early pregnancy, blood flow in the uterine arteries typically has a high systolic flow and low diastolic flow, with the presence of an early diastolic ‘notch’ seen on Doppler ultrasound. In normal pregnancies, as pregnancy progresses, there is a decrease in resistance to blood flow and the notch disappears around 18-24 weeks of gestation. Two commonly used blood flow resistance indices include the pulsatility (peak systolic flow minus end diastolic flow divided by mean flow) and the resistance index (peak systolic flow minus end diastolic flow divided by peak systolic flow), with higher values denoting a lower diastolic flow [17, 179]. High uterine and umbilical flow resistance and notching have been shown to be predictive of a range of pregnancy

complications and adverse fetal outcomes, most notably pre-eclampsia and IUGR [17, 21–23, 25, 180].

It is plausible that air pollution contributes to impaired placental vascular resistance as studies have shown that air pollution up-regulates endothelin, a vasoconstrictor, and increases plasma viscosity, though no studies have examined this specifically in pregnant women [90, 181]. Furthermore, animal studies have also shown that air pollution can cause changes in placental morphology that could contribute to increased placental vascular resistance [182, 183]. Studies on the effect of prenatal air pollution and placental vascular resistance are limited, with only two studies having examined this to date [90, 93]. One study in the Netherlands found no associations between uteroplacental and fetoplacental vascular resistance and PM_{10} and NO_2 exposure in the second and third trimester, but did find an association between NO_2 exposure and 3rd-trimester uterine bilateral notching. The other study, conducted in Brazil, examined uterine and umbilical artery resistance in relation to NO_2 and O_3 exposure in the 3rd trimester, and found that higher levels of O_3 during the 2nd trimester were associated with higher umbilical artery pulsatility indices, but paradoxically higher levels during the 3rd trimester were associated with lower pulsatility.

The impact of smoking during pregnancy on placental vascular resistance has been more frequently studied, however there remains a lack of consensus on which vascular beds of the placenta are affected and whether effects are acute or chronic. Studies have found more support for an increased vascular resistance in the umbilical than in the uterine arteries in response to maternal smoking, thus it has been hypothesized that smoking might have a greater influence on vasculature in the placental villi and a smaller impact on the uteroplacental blood supply [26–29, 97, 98]. It is plausible that smoking results in reduced blood flow as nicotine has been shown to

have vasoconstrictive effects on the uterine and umbilical artery as well as cause structural changes in the placenta that decrease vascularization [184, 185].

The purpose of this study is to elucidate how air pollution and active smoking may have affected placental vascular resistance measured via ultrasound examinations in early, mid and late pregnancy in a multi-ethnic sample of pregnant women living in Los Angeles in the mid 1990s.

4.3 Methods

Study population

Our study population was drawn from the Behavior in Pregnancy Study, which enrolled 688 ethnically and socioeconomically diverse women from private practices and prenatal clinics between 1993 and 1996 in Los Angeles, California [186]. Briefly, this prospective study recruited healthy women ages 18 years or older, less than 20 weeks pregnant and intending to deliver at the study hospital, Cedars-Sinai Medical Center, and followed them to delivery. A comprehensive questionnaire was administered at 3 gestational ages: visit 1 (18-20 weeks' gestation), visit 2 (28-30 weeks' gestation), and visit 3 (35-37 weeks' gestation). Detailed demographic information, socioeconomic status, maternal residence address, and pregnancy history were obtained at baseline (visit1) while information on medical conditions or maternal behaviors including smoking status was collected at each visit. From among 688 mothers, 639 gave birth to a live infant and 578 completed one or more study visits. Mothers with a twin pregnancy (n=4) and stillbirths (n=2), and infants with birth weight <500 grams (n=5) or gestational age >308 days (n=1) were excluded, thus leaving 566 women for our analyses.

Placental Vascular Resistance

At each visit, real-time Doppler velocimetry was conducted to measure placental vascular blood flow using an ATL, HDI 3000 Ultrasound machine (Philips Medical System, the

Netherlands). Doppler measurements were performed on the umbilical artery, and the left and right proximal uterine artery at each visit. These measurements were obtained by one of five sonographers trained and supervised by the project PI (CH). Measurements on each uterine artery were obtained to the point near the cross-over with the internal or external iliac artery. For each waveform, the peak systolic (S) and end diastolic (D) velocities were measured three times, and mean value of these three measurements were calculated. We calculated three related flow indices [19, 20]: the resistance index (RI=(S-D)/S), the pulsatility index (PI=(S-D)/mean velocity), and the S/D ratio. We found no difference between left and right uterine artery RI, thus, we averaged values for both sides (left and right uterine artery RI) at each visit for each participant. The presence of uterine notching was also assessed at each visit. Only 2 participants showed umbilical notching, thus we could not analyze this outcome.

Traffic-related Air Pollution Exposure

Exposures to traffic-related air pollutants were assessed at participants' residential address reported at baseline (visit 1). Addresses were geocoded using three methods including: 1) geocoded to the parcel level using the TeleAtlas Address Point database (n=406); 2) geocoded using address interpolation via the TeleAtlas EZ Locate geocoding service (n=117); and 3) geocoded using Google Earth (n=38, equivalent to highest quality matching using EZ Locate). Five addresses could not be mapped resulting in missing air pollution assignments.

Individual exposures to nitrogen monoxide (NO), NO_2 and NO_x during pregnancy were estimated at residential locations from land use regression (LUR) model surfaces, which provide spatial but not temporal contrasts. The method of creating LUR surfaces has been previously described in detail [187]. Briefly, LUR surfaces for NO, NO_2 and NO_x measures were based on two-week average Ogawa passive diffusion samplers at 181 locations (196 samplers in total)

collecting data simultaneously throughout LA County in September 2006 and February 2007. The final LUR regressions including predictors of traffic volumes, truck routes and road network, land use data, coordinates of the sampling sites, and satellite-derived soil brightness, in which models explained 81%, 86%, and 85% of the variance in measured NO, NO_2, and NO_x concentrations, respectively. LUR NO, NO_2 and NO_x are highly correlated, thus we used NO_2 only as our indicator of traffic related pollution.

Statistical Analysis

We used linear regression models to assess the association between LUR NO_2 per 10 $\mu g/m^3$ and placental vascular resistance indices in standard deviation (SD) values (resistance index/SD of resistance index) at each study visit. We also used logistic regression models to estimate the association between LUR NO_2 and a resistance index above the 90^{th} percentile as uterine resistance values above the 90^{th} percentile have been shown to be predictive of preeclampsia and IUGR [188, 189]. Logistic regression modes were also used to examine the association between LUR NO_2 and the presence of notching in the uterine artery. Based on our review of the literature and directed acyclic graphs (DAGs), we adjusted for the following continuous (gestational weeks at visit, maternal age at delivery, pre-pregnancy body mass index, parity) and categorical covariates (race (white vs nonwhite), education (<12, 12, >12) infant sex, marital status (single, separated, divorced, widowed vs married), prenatal care payment (government vs private), and maternal smoking (former smoker vs ever smoked during pregnancy vs never smoker) [28, 190]. In order to assess smoking as an independent risk factor for placental vascular resistance and notching, we examined smoking (former smoker vs never smoker and smoked during pregnancy vs never smoker) using linear regression models for resistance index values in SD and logistic regression models for resistance index values above

the 90th percentile and presence of uterine notching, adjusting for LUR NO_2 and the aforementioned covariates. Women who were categorized as former smokers reported having ever smoked, but no smoking in the three months prior to pregnancy and during pregnancy. Thus, we had no way to differentiate between women who had at some point in time smoked regularly vs. women who had only ever tried cigarettes. Women who were classified as having smoked during pregnancy reported smoking in the three months prior to pregnancy or at any time during pregnancy.

We also conducted additional sensitivity analyses for the effect of LUR NO_2 by limiting our analyses to non-obese women, women with no uterine notching, and women with no infections during pregnancy. We also examined associations for LUR NO_2 among subgroups of smokers: never smokers, former smokers, and smokers. We conducted analyses stratified by race/ethnicity for the groups for which we had sufficient sample size (White, Hispanic, and African American).

4.4 Results

Demographic characteristics of our study population are reported in Table 4.1. Table 4.2 displays mean and standard deviation values for the placental vascular resistance indices as well as the proportion of women with uterine notching at each study visit. The estimates for the effect of LUR-derived NO_2 per $\mu g/m^3$ and placental vascular resistance indices and notching are shown in Tables 4.3 and 4.4. LUR NO_2 increased the uterine pulsatility, resistance, and S/D ratio in the third exam (β=0.17 SD, 95% CI: (0.05, 0.30); β=0.19 SD, 95% CI: 0.05, 0.32; β=0.18 SD, 95% CI: 0.05, 0.31) per 10 $\mu g/m^3$, respectively]. LUR NO_2 was also associated with an increased risk of uterine pulsatility, resistance, and S/D ratio values above the 90th percentile at the third exam [OR=1.78, 95%CI: 1.13, 2.78; OR=1.70, 95% CI: 1.08, 2.67; OR= 1.96, 95% CI: 1.25, 3.08,

respectively]. None of these resistance measures was however related to air pollution in earlier trimesters.

In air pollution sensitivity analyses, the estimates at the third exam for uterine resistance indices among non-obese women, women with no uterine notching, and women with no infections during pregnancy were similar to those for the total population (data not shown). Risks were also elevated for the uterine resistance indices at the first exam among women without uterine notching, especially for the S/D ratio, but this was based on small numbers (n=5 above the 90^{th} percentile) [OR= 6.24, 95% CI: (1.29 to 30.28)]. When stratifying by smoking status, in the third exam NO_2 increased uterine resistance among never smokers , unilateral notching risk among former smokers [OR=2.59, 95% CI: (1.05 to 6.36)], and bilateral notching risk among current smokers [OR=5.95, 95% CI: 1.67, 21.21]. NO_2 also appeared to increase uterine resistance in the first exam among never smokers though confidence intervals included the null [Tables A 4.1, A 4.2].

When stratified by race/ethnicity, Whites and Hispanics showed patterns similar to our overall sample, with increased uterine resistance with NO_2 exposure in the third exam, however resistance index estimates for African American women were largely null while these women however had an increased risk of unilateral uterine notching [OR=2.64, 95% CI: (1.23, 5.66)] [Tables A 4.3 and A 4.4]

Examining the impact of smoking while adjusting for LUR NO_2 exposures and other covariates on placental vascular resistance, we found that solely being a former smoker increased the risk of umbilical pulsatility, resistance, and S/D ratio values above the 90^{th} percentile in the third exam (OR=2.74, 95% CI: 1.26, 5.98; OR=2.66, 95% CI: 1.22, 5.80; OR=2.43, 95% CI: 1.10, 5.37). For the uterine artery, being a former smoker appeared to elevate risks of higher resistance values most at the second and third exam (in mid and late pregnancy), but all

confidence intervals crossed the null. Smoking at any point during pregnancy increased umbilical artery pulsatility and resistance index values per SD at the second exam in mid pregnancy [β=(0.26, 95% CI: 0.03, 0.50), β =(0.25, 95% CI 0.02, 0.48), respectively]. Similarly, for the uterine artery, smoking during pregnancy increased pulsatility, resistance, and S/D values in SD and having values above the 90th percentile at the second exam, particularly for the pulsatility index. Smoking during pregnancy also increased the risk of uterine bilateral notching at the second exam [OR=2.02, 95% CI: 1.19, 3.43] [Tables 4.5 and 4.6].

4.5 Discussion

In this study, we found that maternal traffic-related air pollution exposure increased the risk of high uterine artery resistance in late pregnancy (35-37 weeks). These results were the same when we restricted to non-obese women, those without uterine notching and infections during pregnancy, and never smokers. Interestingly, among former and current smokers, NO_2 exposure did not increase risk of placental vascular resistance indices, however, we did find an increased risk of notching with air pollution at the third exam. Additionally, we also did not find any air pollution associations with placental vascular resistance among African American women, but again found an increased risk of notching at the third exam. For smoking we found that being a former smoker increases umbilical resistance indices in the third exam while smoking during pregnancy increases the risk of higher umbilical and uterine resistance values, as well as uterine bilateral notching at the second exam.

Only two other studies have examined the effect of air pollution on uterine artery resistance and they found no association with NO_2 exposure in the third trimester [90, 93]. One of the two studies that examined the association between NO_2 exposure and notching found an increased risk with bilateral notching [93]. One potential explanation for the null findings in

other studies for NO_2 exposure, in contrast to ours, is that these studies looked at the early third trimester (mean or median of 31 weeks). The effects of air pollution may not manifest until the late third-trimester since our estimates for the second exam, which were taken in earlier part of the third trimester (28-30 weeks) were largely null. Additionally, air pollution exposures throughout pregnancy may have a cumulative effect on blood flow resistance and these might be most pronounced and notable towards the end of pregnancy. Of note, our LUR model based NO2 measures are pregnancy averages since this type of exposure assessment emphasizes spatial over temporal variations. There is no consensus on which period during pregnancy is most susceptible to the effects of air pollution, but the evidence in the literature suggests effects slightly stronger for the first and third trimester [91]. Studies have shown that increased placental vascular resistance indices throughout pregnancy and notching are strong predictors of adverse pregnancy outcomes, particularly for the uterine artery and bilateral uterine notching [22, 28]. One study examined the association between NO_2 in Western Australia using an LUR model and found that the risk of pre-eclampsia was strongest in the third trimester [191]. We were unable to assess the effect of exposures in the first trimester as our first study visit occurred between 18-20 weeks of gestation, however since typically vascular resistance decreases and notching disappears around 18-24 weeks of gestation in normal pregnancies, it is the presence of elevated resistance indices and notching after this period that are most strongly associated with adverse pregnancy outcomes [21, 192].

The lack of findings for the resistance indices in former/current smokers and African American women compelled us to investigate the resistance patterns and birth outcomes in these subgroups in more detail and we hypothesized that air pollution associations in these women might be harder to detect if they either already have much higher placental vascular resistance

and/or are at higher risk of fetal loss. Several studies have shown that smoking increases placental blood flow and vascular resistance and notching [26, 27, 29]. Additionally, smokers are more likely to have an increased risk of fetal loss [193] and preterm birth [22, 96]. In fact, we observed that in our study the number of smokers decreased over follow-up from 95 to 88 former smokers by visit 3 with 7 of these 9 infants being born preterm. For those who smoked during pregnancy the number of smokers decreased from 103 to 81 by visit 3 and more than half of those who dropped out were preterm births (13 of the 23). Thus, this loss to follow-up of fetuses impacted by smoking may account for the lack of estimated air pollution effects at the third visit since women at highest risk were not available anymore for a third visit during pregnancy. Additionally, this may also at least partially explain why we did not see any association of the resistance indices with air pollution in late pregnancy for African American women, they were at greatest risk of preterm delivery and 34 out of 238 African American women (14%) delivered preterm [22, 96]. Early fetal loss or miscarriage could also be impacting our results. Since smoking has been associated with an increased risk of placental vascular resistance and miscarriage, and our study includes only live born children, this could induce collider-stratification bias which would negatively confound the association between NO_2 exposure and placental vascular resistance [194]. By conditioning on smoking, we attempted to address this potential bias, though the possibility of residual confounding remains since smoking was collected by self-report.

For smoking, we confirmed previous findings of an increased risk of umbilical and uterine resistance indices and notching for women who actively smoked during pregnancy [26, 27, 29]. These effects were largely seen in mid pregnancy i.e. at the second exam. For former smokers, estimated effects on placental vascular resistance were largely limited to the umbilical

artery resistance indices in late pregnancy i.e. at the third exam. No other studies to our knowledge have compared the effects of being a former smoker vs current smoker on placental vascular resistance. We might expect former smokers to have a less risky health profile than women who continued smoking during pregnancy as various studies have found that former smokers are more likely to be primiparous, privately insured and college-educated [195]. This is similar to our sample as former smokers were more likely to be older, White, nulliparous, and have higher education and socioeconomic status. Our results suggest that umbilical resistance indices are higher late in pregnancy in former smokers, but we do not know whether this was due to reporting bias (women did indeed smoke during pregnancy as well) or chronic effects of having been smoking among those who quit prior to pregnancy. For instance, women who quit smoking have been found to have higher weight gain as well as an increased risk of hypertension compared to continuing smokers or never smokers [196]. A study that examined misclassification of self-reported smoking us cotinine measurements found that 24% of active smokers were misclassified as quitters because they inaccurately reported that they had quit or relapsed by mid-pregnancy. Furthermore, women who were misclassified as quitters were more likely to report that they quit during rather than before pregnancy [95]. In our study, former smokers were women who reported smoking in the 3 months prior to pregnancy but not during pregnancy, and current smokers were those who reported smoking at any point during pregnancy, thus by classifying smokers in this manner we may have minimized this potential bias.

There were several strengths and limitations of our study. Since our LUR spatial pollution surfaces were developed more than a decade after the placental vascular resistance measures were obtained in this pregnancy cohort, we relied on the assumption that on average

the spatial relations between high and low traffic pollution areas remained stable. This could introduce non-differential exposure misclassification if this assumption is incorrect. Furthermore, since we relied on address reported at baseline of the study to generate the pollution measures, thus this could introduce non-differential misclassification as well if women moved during pregnancy, most likely for exposure received in later pregnancy. Also, we did not have enough information on time-activity to account for higher or lower personal exposures for women at work and away from their residences during pregnancy introducing additional potential for exposure misclassification. If women however did not move and stayed at home more often towards the very end of their pregnancies, as has previously been observed [197], this would reduce exposure misclassification due to time-activity in the third period and potentially explain why we find stronger associations in the last pregnancy period. Some effects observed may be due to chance due to small sample sizes in our subgroup analyses, however the effects of the LUR derived NO_2 exposures on uterine and resistance indices at the third exam were very robust in all sensitivity analyses. Some strengths of this study include the ethnically and socioeconomically diverse sample for which we had detailed covariate information. Additionally, few studies to date have examined these measures of uterine and umbilical placental resistance in relation to air pollution. Of these studies, this is the first to also take into account the impact of smoking on these indices and especially the resultant greater loss to follow-up during pregnancy such as via preterm delivery in smokers.

In conclusion, we found an increased risk of placental vascular resistance indices with exposure to traffic-related air pollution in late pregnancy and associations with active and former smoking mid- and late pregnancy. Our results suggest that air pollution adversely impacts placental vascular resistance which may help explain the increased risk of adverse pregnancy and

birth outcomes previously associated with air pollution. Nevertheless, further studies of susceptible time periods and mechanisms underlying this association are warranted. Additionally, attention to the impact of smoking when assessing the effect of air pollution on placental vascular resistance has been understudied to date, and further investigation is warranted as smoking appears to be an independent risk factor for higher placental vascular resistance and preterm birth, even among mothers reporting quitting prior to pregnancy.

4.6 Tables

Table 4.1. Baseline characteristics of the study population	
Maternal Characteristics	Mean ± SD or n (%)
Maternal age (years)	
<20	32 (5.7)
20-24	147 (26.0)
25-29	178 (31.3)
30-34	152 (26.9)
≥35	57 (10.1)
Maternal race/ethnicity	
White, non-Hispanic	124 (21.9)
Hispanic	173 (30.6)
African American	238 (42.0)
Asian	24 (4.3)
Other	7 (1.2)
Maternal education (years)	
<12	92 (16.3)
12	189 (33.4)
>12	285 (50.4)
Marital status	
Single, separated, divorced or widowed	276 (48.8)
Married	290 (51.2)
Parity	
Nulliparous	220 (38.9)
Multiparous	346 (61.1)
Source of care payment	
Government assisted insurance[a]	263 (46.5)
Private insurance (HMO or Other)	303 (53.5)
Infant's sex	
Male	287 (50.7)
Female	279 (49.3)
Maternal smoking during pregnancy	
First pregnancy period	
Yes	102 (18.0)
No	463 (81.8)
Missing	1 (0.2)
Second pregnancy period	
Yes	30 (5.3)
No	513 (90.6)
Missing	23 (4.1)
Third pregnancy period	

Yes	18 (3.2)
No	459 (81.1)
Missing	89 (15.7)
Maternal infections	
First pregnancy period	
Yes	222 (39.2)
No	343 (60.6)
Missing	1 (0.2)
Second pregnancy period	
Yes	108 (19.1)
No	434 (76.7)
Missing	24 (4.2)
Third pregnancy period	
Yes	91 (15.7)
No	386 (68.2)
Missing	89 (15.7)
Maternal height (m) (n=560)	1.63 (0.07)
Maternal pre-pregnancy weight (kg) (n=565)	67.4 (17.6)
Maternal pregnancy weight gain (kg)	
First pregnancy period (n=565)	5.4 (5.0)
Second pregnancy period (n=543)	4.9 (2.8)
Third pregnancy period (n=477)	4.0 (2.6)
Gestational age at birth (days)	273.8 (16.0)

Table 4.2 Characteristics of placental vascular resistance at each visit		
Placental vascular resistance	N	Mean ± SD or n (%)
Visit 1, gestational age at first visit	560	19.2 (0.9)
Umbilical artery pulsatility index	554	1.20 (0.17)
Umbilical artery resistance index	554	0.75 (0.07)
Umbilical artery S/D ratio	546	4.14 (1.07)
Uterine artery pulsatility index	558	0.74 (0.18)
Uterine artery resistance index	558	0.53 (0.09)
Uterine artery S/D ratio	558	2.39 (0.77)
Presence of unilateral uterine artery notching	553	133 (24.05)
Presence of bilateral uterine artery notching	553	230 (41.59)
Visit 2, gestational age at second visit	542	28.8 (0.8)
Umbilical artery pulsatility index	538	0.99 (0.16)
Umbilical artery resistance index	538	0.66 (0.07)
Umbilical artery S/D ratio	535	3.02 (0.68)
Uterine artery pulsatility index	539	0.61 (0.14)
Uterine artery resistance index	539	0.46 (0.08)
Uterine artery S/D ratio	539	1.99 (0.44)
Presence of unilateral uterine artery notching	536	124 (23.13)
Presence of bilateral uterine artery notching	536	128 (23.88)
Visit 3, gestational age at third visit	486	36.7 (0.7)
Umbilical artery pulsatility index	482	0.80 (0.13)
Umbilical artery resistance index	482	0.57 (0.07)
Umbilical artery S/D ratio	482	2.38 (0.41)
Uterine artery pulsatility index	486	0.59 (0.13)
Uterine artery resistance index	486	0.45 (0.07)
Uterine artery S/D ratio	486	1.92 (0.34)
Presence of unilateral uterine artery notching	485	117 (24.12)
Presence of bilateral uterine artery notching	485	116 (23.92)

Table 4.3 Effect estimates for LUR NO2 (per 10 µg/m3) and umbilical artery resistance

	Visit 1			Visit 2			Visit 3		
	n: ≥/ <90th	Crude model	Model 1[a]	n: ≥/ <90th	Crude model	Model 1[a]	n: ≥/ <90th	Crude model	Model 1[a]
Pulsatility index									
Per SD (Beta, 95%CI)		0.03 (-0.09, 0.15)	0.02 (-0.11, 0.14)		-0.02 (-0.14, 0.10)	-0.01 (-0.14, 0.12)		0.11 (-0.02, 0.24)	0.08 (-0.06, 0.21)
≥ vs. <90th percentile (Odds ratio, 95% CI)	55/499	1.00 (0.68, 1.48)	0.99 (0.63, 1.55)	53/485	1.05 (0.71, 1.56)	1.09 (0.71, 1.66)	48/434	1.45 (0.95, 2.20)	1.29 (0.78, 2.13)
Resistance index									
Per SD (Beta, 95%CI)		0.03 (-0.08, 0.14)	0.02 (-0.09, 0.14)		-0.02 (-0.14, 0.10)	-0.01 (-0.13, 0.12)		0.11 (-0.02, 0.23)	0.08 (-0.05, 0.21)
≥ vs. <90th percentile (Odds ratio, 95% CI)	55/499	1.00 (0.68, 1.48)	0.99 (0.63, 1.55)	54/484	1.05 (0.71, 1.55)	1.07 (0.70, 1.63)	49/433	1.46 (0.96, 2.22)	1.33 (0.81, 2.18)
S/D ratio									
Per SD (Beta, 95%CI)		0.08 (-0.04, 0.20)	0.09 (-0.03, 0.21)		-0.02 (-0.10, 0.14)	0.04 (-0.08, 0.16)		0.10 (-0.02, 0.23)	0.07 (-0.06, 0.20)
≥ vs. <90th percentile (Odds ratio, 95% CI)	54/492	1.10 (0.75, 1.62)	1.19 (0.77, 1.85)	53/482	1.10 (0.74, 1.63)	1.10 (0.72, 1.68)	48/434	1.49 (0.98, 2.24)	1.31 (0.79, 2.16)
Presence of notching									
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA	NA	NA	NA

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, maternal smoking

Table 4.4 Effect estimates for LUR NO2 (per 10 µg/m3) and uterine artery resistance

	Visit 1			Visit 2			Visit 3		
	n: ≥/ <90th	Crude model	Model 1[a]	n: ≥/ <90th	Crude model	Model 1[a]	n: ≥/ <90th	Crude model	Model 1[a]
Pulsatility index									
Per SD (Beta, 95%CI)		0.00 (-0.11, 0.12)	0.03 (-0.10, 0.15)		0.06 (-0.06, 0.18)	0.06 (-0.07, 0.18)		0.16 (0.03, 0.28)	0.17 (0.05, 0.30)
≥ vs. <90th percentile (Odds ratio, 95% CI)	56/502	1.13 (0.77, 1.66)	1.13 (0.74, 1.71)	53/486	1.03 (0.70, 1.53)	1.01 (0.66, 1.53)	49/437	1.73 (1.14, 2.63)	1.78 (1.13, 2.78)
Resistance index									
Per SD (Beta, 95%CI)		0.01 (-0.11, 0.13)	0.03 (-0.10, 0.16)		0.06 (-0.05, 0.18)	0.06 (-0.06, 0.18)		0.17 (0.04, 0.29)	0.19 (0.05, 0.32)
≥ vs. <90th percentile (Odds ratio, 95% CI)	56/502	1.06 (0.72, 1.55)	1.08 (0.72, 1.64)	54/485	0.90 (0.61, 1.33)	0.84 (0.55, 1.29)	48/438	1.65 (1.08, 2.51)	1.70 (1.08, 2.67)
S/D ratio									
Per SD (Beta, 95%CI)		-0.04 (-0.14, 0.07)	-0.02 (-0.13, 0.09)		0.05 (-0.07, 0.17)	0.05 (-0.07, 0.17)		0.16 (0.03, 0.29)	0.18 (0.05, 0.31)
≥ vs. <90th percentile (Odds ratio, 95% CI)	55/503	1.14 (0.78, 1.68)	1.20 (0.79, 1.83)	54/485	1.07 (0.72, 1.57)	1.05 (0.69, 1.59)	48/438	1.83 (1.21, 2.78)	1.96 (1.25, 3.08)
Presence of notching									
Unilateral (Odds ratio, 95% CI)	133/420	1.09 (0.83, 1.44)	1.03 (0.77, 1.40)	124/412	1.04 (0.79, 1.37)	1.06 (0.78, 1.42)	117/368	1.08 (0.80, 1.45)	1.20 (0.87, 1.65)
Bilateral (Odds ratio, 95% CI)	230/323	1.02 (0.80, 1.29)	1.12 (0.86, 1.46)	128/408	0.90 (0.68, 1.19)	0.94 (0.70, 1.28)	116/369	1.14 (0.85, 1.53)	1.19 (0.86, 1.65)

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, maternal smoking

Table 4.5 Effect estimates for smoking and umbilical artery resistance						
	Visit 1		Visit 2		Visit 3	
Former smoker vs never smoked (n=97)						
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		0.18 (-0.06, 0.41)		0.05 (-0.19, 0.29)		0.14 (-0.11, 0.39)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/83	1.56 (0.73, 3.34)	9/84	0.98 (0.43, 2.23)	13/75	**2.74 (1.26, 5.98)**
Resistance index						
Per SD (Beta, 95%CI)		0.15 (-0.06, 0.37)		0.06 (-0.18, 0.29)		0.13 (-0.11, 0.37)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/83	1.56 (0.73, 3.34)	9/84	0.96 (0.42, 2.17)	13/75	**2.66 (1.22, 5.80)**
S/D ratio						
Per SD (Beta, 95%CI)		0.16 (-0.07, 0.39)		0.02 (-0.22, 0.26)		0.14 (-0.10, 0.38)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/82	1.29 (0.59, 2.81)	9/84	0.97 (0.43, 2.20)	12/76	**2.43 (1.10, 5.37)**
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Smoked during pregnancy vs never smoked (n=104)						
Pulsatility index						
Per SD (Beta, 95%CI)		0.10 (-0.13, 0.33)		**0.26 (0.03, 0.50)**		0.18 (-0.07, 0.44)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/91	1.43 (0.67, 3.05)	12/90	1.23 (0.59 to 2.60)	3/78	0.44 (0.12, 1.55)
Resistance index						
Per SD (Beta, 95%CI)		0.10 (-0.11, 0.31)		**0.25 (0.02, 0.48)**		0.19 (-0.05, 0.44)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/91	1.43 (0.67, 3.05)	12/90	1.21 (0.58, 2.56)	3/78	0.44 (0.12, 1.55)
S/D ratio						
Per SD (Beta, 95%CI)		0.11 (-0.12, 0.33)		0.12 (-0.11, 0.35)		0.12 (-0.12, 0.37)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/90	1.43 (0.66, 3.10)	11/89	1.14 (0.53, 2.45)	3/78	0.43 (0.12, 1.52)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, LUR NO_2

Table 4.6 Effect estimates for smoking and uterine artery resistance						
	Visit 1		Visit 2		Visit 3	
Former smoker vs never smoked (n=97)						
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		0.04 (-0.19, 0.27)		0.19 (-0.05, 0.43)		0.03 (-0.20, 0.26)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/85	1.13 (0.53, 2.38)	11/83	**1.82 (0.82, 4.01)**	11/77	**1.62 (0.73, 3.58)**
Resistance index						
Per SD (Beta, 95%CI)		0.05 (-0.19, 0.29)		0.18 (-0.05, 0.41)		0.00 (-0.24, 0.25)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/86	0.97 (0.45, 2.08)	11/83	**2.03 (0.92 to 4.49)**	10/78	**1.86 (0.83, 4.19)**
S/D ratio						
Per SD (Beta, 95%CI)		0.06 (-0.16, 0.27)		0.20 (-0.04 to 0.44)		0.11 (-0.14, 0.35)
≥ vs. <90th percentile (Odds ratio, 95% CI)	13/84	1.40 (0.67, 2.92)	11/83	**1.61 (0.74 to 3.50)**	12/76	**1.51 (0.69, 3.31)**
Presence of notching						
Unilateral (Odds ratio, 95% CI)	23/73	1.01 (0.58, 1.77)	16/77	0.57 (0.31, 1.07)	23/65	1.01 (0.57, 1.80)
Bilateral (Odds ratio, 95% CI)	43/53	1.01 (0.61, 1.66)	25/68	1.37 (0.78, 2.42)	22/66	0.95 (0.53, 1.71)
Smoked during pregnancy vs never smoked (n=104)						
Pulsatility index						
Per SD (Beta, 95%CI)		0.01 (-0.21, 0.24)		**0.24 (0.01, 0.47)**		0.03 (-0.20, 0.26)
≥ vs. <90th percentile (Odds ratio, 95% CI)	9/95	0.66 (0.28, 1.56)	17/85	**2.14 (1.06, 4.34)**	9/74	1.38 (0.57, 3.34)
Resistance index						
Per SD (Beta, 95%CI)		0.01 (-0.22, 0.25)		**0.21 (-0.01, 0.44)**		-0.01 (-0.26, 0.24)
≥ vs. <90th percentile (Odds ratio, 95% CI)	9/95	0.69 (0.29, 1.62)	19/83	**2.64 (1.32, 5.27)**	10/73	1.64 (0.70, 3.85)
S/D ratio						
Per SD (Beta, 95%CI)		-0.02 (-0.23, 0.19)		**0.24 (0.01, 0.47)**		0.08 (-0.17, 0.33)
≥ vs. <90th percentile (Odds ratio, 95% CI)	10/94	0.94 (0.41, 2.15)	14/88	**1.52 (0.74, 3.14)**	8/75	1.15 (0.46, 2.88)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	21/82	0.75 (0.42, 1.33)	19/83	0.65 (0.36, 1.16)	14/68	0.72 (0.37, 1.39)
Bilateral (Odds ratio, 95% CI)	46/57	1.05 (0.64, 1.71)	35/67	**2.02 (1.19, 3.43)**	18/64	0.78 (0.42, 1.47)

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, LUR NO_2

Appendix 4.7

Table A 4.1 Effect estimates for smoking and umbilical resistance by smoking status						
Among never smokers						
	Visit 1		Visit 2		Visit 3	
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		-0.02 (-0.16, 0.13)		0.11 (-0.04, 0.26)		0.15 (-0.03, 0.32)
≥ vs. <90th percentile (Odds ratio, 95% CI)	31/324	0.81 (0.44, 1.49)	32/310	1.41 (0.83, 2.40)	32/280	1.31 (0.67, 2.56)
Resistance index						
Per SD (Beta, 95%CI)		-0.01 (-0.15, 0.12)		0.12 (-0.03, 0.27)		0.15 (-0.02, 0.31)
≥ vs. <90th percentile (Odds ratio, 95% CI)	31/324	0.81 (0.44, 1.49)	33/309	1.38 (0.81, 2.34)	33/279	1.38 (0.71, 2.66)
S/D ratio						
Per SD (Beta, 95%CI)		0.04 (-0.10, 0.19)		0.15 (-0.01, 0.31)		0.11 (-0.05, 0.28)
≥ vs. <90th percentile (Odds ratio, 95% CI)	32/319	1.02 (0.58, 1.78)	33/308	1.44 (0.85, 2.45)	33/279	1.29 (0.67, 2.50)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Among former smokers						
Pulsatility index						
Per SD (Beta, 95%CI)		0.05 (-0.30, 0.40)		-0.17 (-0.45, 0.11)		-0.06 (-0.49, 0.28)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/83	1.34 (0.46, 3.89)	9/84	1.92 (0.51, 7.20)	13/75	1.98 (0.55, 7.08)
Resistance index						
Per SD (Beta, 95%CI)		0.09 (-0.23, 0.41)		-0.19 (-0.48, 0.10)		-0.08 (-0.40, 0.24)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/83	1.34 (0.46, 3.89)	9/84	1.91 (0.51, 7.20)	13/75	1.98 (0.55, 7.08)
S/D ratio						
Per SD (Beta, 95%CI)		0.32 (-0.01, 0.65)		-0.12 (-0.38, 0.14)		0.00 (-0.33, 0.33)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/82	2.01 (0.60, 6.68)	9/84	1.92 (0.51, 7.20)	13/75	3.14 (0.72, 13.78)[b]
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Among smokers						
Pulsatility index						

Per SD (Beta, 95%CI)		0.30 (-0.00, 0.60)		-0.04 (-0.39, 0.31)		0.23 (-0.05, 0.50)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/91	2.19 (0.63, 7.61)[b]	12/90	0.20 (0.03, 1.22)[b]	3/78	NE
Resistance index						
Per SD (Beta, 95%CI)		0.27 (0.00, 0.56)		-0.04 (-0.35, 0.28)		0.22 (-0.04, 0.48)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/91	2.19 (0.63, 7.61)[b]	12/90	0.20 (0.03, 1.22)	3/78	NE
S/D ratio						
Per SD (Beta, 95%CI)		0.29 (0.02, 0.56)		-0.05 (-0.31, 0.20)		0.21 (-0.04, 0.47)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/90	1.75 (0.53, 5.76)[b]	11/89	0.17 (0.02, 1.12)[b]	3/78	NE
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, LUR NO_2

[b]SAS warning: validity of model questionable, potential quasi-separation

Table A 4.2. Effect estimates for smoking and uterine resistance by smoking status						
Among never smokers						
	Visit 1		Visit 2		Visit 3	
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		0.07 (-0.07, 0.22)		0.09 (-0.05, 0.23)		0.20 (0.06, 0.35)
≥ vs. <90th percentile (Odds ratio, 95% CI)	35/321	1.54 (0.93, 2.55)	25/317	1.13 (0.65, 1.96)	29/285	1.89 (1.06, 3.37)
Resistance index						
Per SD (Beta, 95%CI)		0.07 (-0.08, 0.23)		0.09 (-0.05, 0.23)		0.22 (0.06, 0.37)
≥ vs. <90th percentile (Odds ratio, 95% CI)	36/320	1.55 (0.94, 2.55)	24/318	0.97 (0.55, 1.73)	28/286	1.84 (1.03, 3.30)
S/D ratio						
Per SD (Beta, 95%CI)		0.03 (-0.11, 0.16)		0.09 (-0.04, 0.22)		0.20 (0.05, 0.34)
≥ vs. <90th percentile (Odds ratio, 95% CI)	32/324	1.62 (0.96, 2.72)	29/313	1.17 (0.69, 1.98)	28/286	2.08 (1.17, 3.71)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	89/264	0.98 (0.68, 1.42)	NA	1.00 (0.70, 1.43)	80/234	1.24 (0.83, 1.84)
Bilateral (Odds ratio, 95% CI)	140/213	1.15 (0.82, 1.60)	NA	1.04 (0.70, 1.54)	76/238	0.96 (0.65, 1.44)
Among former smokers						
Pulsatility index						
Per SD (Beta, 95%CI)		-0.02 (-0.32, 0.29)		0.09 (-0.25, 0.44)		0.23 (-0.14, 0.59)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/85	0.83 (0.23, 2.93)	11/83	2.44 (0.76, 7.83)	11/77	2.38 (0.74, 7.64)
Resistance index						
Per SD (Beta, 95%CI)		-0.02 (-0.32, 0.28)		0.08 (-0.24, 0.40)		0.23 (-0.15, 0.61)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/86	0.77 (0.20, 2.95)	11/83	2.44 (0.76, 7.83)	10/78	2.33 (0.69, 7.88)
S/D ratio						
Per SD (Beta, 95%CI)		-0.04 (-0.35, 0.27)		0.07 (-0.29, 0.44)		0.26 (-0.13, 0.65)
≥ vs. <90th percentile (Odds ratio, 95% CI)	13/84	1.34 (0.46, 3.93)	11/83	2.44 (0.76, 7.83)	12/76	1.82 (0.60, 5.51)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	23/73	1.26 (0.54, 2.95)	16/77	0.98 (0.38, 2.55)	23/65	2.59 (1.05, 6.36)
Bilateral (Odds ratio, 95% CI)	43/53	1.37 (0.56, 3.38)	25/68	0.88 (0.38, 2.07)	22/66	1.22 (0.51, 2.92)
Among smokers						
Pulsatility index						

Per SD (Beta, 95%CI)		-0.11 (-0.40, 0.18)		0.01 (-0.34, 0.36)		0.01 (-0.29, 0.31)
≥ vs. <90th percentile (Odds ratio, 95% CI)	9/95	0.25 (0.05, 1.18)[b]	17/85	0.75 (0.28, 2.00)	9/74	0.88 (0.18, 4.35)
Resistance index						
Per SD (Beta, 95%CI)		-0.08 (-0.38, 0.23)		0.02 (-0.32, 0.36)		0.01 (-0.31, 0.33)
≥ vs. <90th percentile (Odds ratio, 95% CI)	9/95	0.15 (0.02, 0.95)[b]	19/83	0.59 (0.22, 1.59)	10/73	0.82 (0.17, 3.97)
S/D ratio						
Per SD (Beta, 95%CI)		-0.21 (-0.47, 0.04)		0.02 (-0.35, 0.39)		-0.02 (-0.38, 0.33)
≥ vs. <90th percentile (Odds ratio, 95% CI)	10/94	0.27 (0.07, 1.06)	14/88	0.67 (0.23, 1.92)	8/75	1.26 (0.23, 7.00)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	21/82	0.61 (0.25, 1.54)	19/83	1.49 (0.58, 3.81)	14/68	0.30 (0.08, 1.11)[b]
Bilateral (Odds ratio, 95% CI)	46/57	1.68 (0.84, 3.35)	35/67	1.19 (0.55, 2.56)	18/64	5.95 (1.67, 21.23)

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, LUR NO_2

[b]SAS warning: validity of model questionable, potential quasi-separation

Table A 4.3 Effect estimates for LUR NO2 (per 10 µg/m3) and umbilical resistance by race						
Among Whites						
	Visit 1		Visit 2		Visit 3	
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		0.19 (-0.05, 0.43)		-0.04 (-0.28, 0.20)		-0.06 (-0.33, 0.21)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/109	1.09 (0.39, 3.06)	13/106	0.30 (0.08, 1.04)	4/101	0.80 (0.03, 24.42)[b]
Resistance index						
Per SD (Beta, 95%CI)		0.17 (-0.05, 0.39)		-0.04 (-0.27, 0.20)		-0.07 (-0.33, 0.19)
≥ vs. <90th percentile (Odds ratio, 95% CI)	12/109	1.13 (0.41, 3.09)	13/106	0.29 (0.08, 1.03)	4/101	1.62 (0.13, 20.50)[b]
S/D ratio						
Per SD (Beta, 95%CI)		0.14 (-0.11, 0.40)		-0.08 (-0.44, 0.28)		-0.04 (-0.27, 0.20)
≥ vs. <90th percentile (Odds ratio, 95% CI)	13/107	0.93 (0.36, 2.40)	13/106	0.29 (0.08, 1.03)	4/101	1.62 (0.13, 20.50)[b]
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Among African Americans						
Pulsatility index						
Per SD (Beta, 95%CI)		-0.14 (-0.37, 0.10)		-0.17 (-0.45, 0.10)		0.04 (-0.24, 0.32)
≥ vs. <90th percentile (Odds ratio, 95% CI)	24/210	1.12 (0.51, 2.48)	23/202	0.73 (0.32, 1.66)	17/177	1.17 (0.38, 3.54)
Resistance index						
Per SD (Beta, 95%CI)		-0.13 (-0.33, 0.08)		-0.17 (-0.42, 0.09)		0.05 (-0.23, 0.32)
≥ vs. <90th percentile (Odds ratio, 95% CI)	24/210	1.09 (0.49, 2.42)	24/201	0.69 (0.31, 1.55)	17/177	1.28 (0.44, 3.77)
S/D ratio						
Per SD (Beta, 95%CI)		-0.02 (-0.24 to 0.20)		-0.07 (-0.28, 0.15)		0.02 (-0.24, 0.29)
≥ vs. <90th percentile (Odds ratio, 95% CI)	22/208	1.29 (0.58, 2.88)	22/200	0.79 (0.34, 1.82)	18/176	1.30 (0.45, 3.69)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Among Hispanics						
Pulsatility index						
Per SD (Beta, 95%CI)		0.15 (-0.08, 0.38)		0.15 (-0.04, 0.35)		-0.01 (-0.25, 0.22)
≥ vs. <90th percentile (Odds ratio, 95% CI)	16/153	1.14 (0.43, 3.07)	15/149	2.28 (0.90, 5.73)[b]	23/133	1.02 (0.46, 2.25)

Resistance index						
Per SD (Beta, 95%CI)		0.16 (-0.06, 0.38)		0.15 (-0.06, 0.36)		-0.01 (-0.23, 0.21)
≥ vs. <90th percentile (Odds ratio, 95% CI)	16/153	1.14 (0.45, 2.91)	15/149	2.02 (0.83, 4.93)	23/133	1.06 (0.51, 2.23)
S/D ratio						
Per SD (Beta, 95%CI)		0.18 (-0.06, 0.41)		0.16 (-0.02, 0.34)		-0.03 (-0.27, 0.22)
≥ vs. <90th percentile (Odds ratio, 95% CI)	16/151	1.27 (0.51, 3.18)	16/148	1.72 (0.73, 4.01)	22/134	1.08 (0.50, 2.34)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA
Bilateral (Odds ratio, 95% CI)	NA	NA	NA	NA	NA	NA

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, maternal smoking

[b]SAS warning: validity of model questionable, potential quasi-separation

Table A 4.4 Effect estimates for LUR NO2 (per 10 µg/m3) and uterine resistance by race						
Among Whites						
	Visit 1		Visit 2		Visit 3	
	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]	n: ≥/ <90th	Model 1[a]
Pulsatility index						
Per SD (Beta, 95%CI)		0.03 (-0.23, 0.29)		0.06 (-0.18, 0.31)		0.10 (-0.15, 0.35)
≥ vs. <90th percentile (Odds ratio, 95% CI)	10/112	1.40 (0.49, 3.98)[b]	6/114	0.75 (0.16, 3.44)[b]	7/100	1.62 (0.53, 4.92)[b]
Resistance index						
Per SD (Beta, 95%CI)		0.04 (-0.23, 0.31)		0.07 (-0.17, 0.32)		0.10 (-0.17, 0.36)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/111	1.29 (0.52, 3.22)[b]	6/114	0.71 (0.17, 2.95)[b]	7/100	1.80 (0.60, 5.34)
S/D ratio						
Per SD (Beta, 95%CI)		-0.01 (-0.26, 0.23)		0.05 (-0.20, 0.29)		0.11 (-0.13, 0.35)
≥ vs. <90th percentile (Odds ratio, 95% CI)	11/111	1.70 (0.58, 5.00)[b]	6/114	0.71 (0.17, 2.95)[b]	10/97	1.65 (0.63, 4.34)[b]
Presence of notching						
Unilateral (Odds ratio, 95% CI)	24/97	1.11 (0.55, 2.25)[b]	24/96	0.88 (0.39, 1.99)	30/41	0.62 (0.31, 1.26)
Bilateral (Odds ratio, 95% CI)	62/59	1.22 (0.66, 2.26)	35/85	1.41 (0.73, 2.71)[b]	28/79	1.72 (0.83, 3.59)[b]
Among African Americans						
Pulsatility index						
Per SD (Beta, 95%CI)		0.07 (-0.15, 0.30)		-0.02 (-0.27, 0.23)		0.07 (-0.18, 0.33)
≥ vs. <90th percentile (Odds ratio, 95% CI)	21/215	1.58 (0.70, 3.53)	29/196	1.10 (0.55, 2.19)	17/178	0.95 (0.33, 2.74)
Resistance index						
Per SD (Beta, 95%CI)		0.06 (-0.17, 0.30)		-0.01 (-0.27, 0.23)		0.07 (-0.20, 0.34)
≥ vs. <90th percentile (Odds ratio, 95% CI)	21/215	1.38 (0.62, 3.10)	32/193	0.89 (0.46, 1.72)	18/177	1.08 (0.37, 3.13)
S/D ratio						
Per SD (Beta, 95%CI)		0.02 (-0.19, 0.24)		-0.06 (0.13, -0.32)		0.13 (-0.15 to 0.40)
≥ vs. <90th percentile (Odds ratio, 95% CI)	21/215	1.99 (0.88, 4.50)	28/197	1.02 (0.51, 2.04)	14/181	1.40 (0.45 to 4.32)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	63/170	0.84 (0.48, 1.47)	54/170	1.36 (0.78, 2.40)	41/154	2.64 (1.23, 5.66)
Bilateral (Odds ratio, 95% CI)	76/157	1.16 (0.69, 1.96)	52/172	1.12 (0.64, 1.96)	42/153	0.76 (0.37, 1.56)
Among Hispanics						
Pulsatility index						
Per SD (Beta, 95%CI)		0.02 (-0.20, 0.25)		0.06 (-0.15, 0.28)		0.25 (0.03, 0.47)
≥ vs. <90th percentile (Odds ratio, 95% CI)	22/148	0.88 (0.42, 1.85)	15/149	1.03 (0.43, 2.48)	23/134	2.18 (1.02, 4.70)

Resistance index						
Per SD (Beta, 95%CI)		0.03 (-0.20, 0.27)		0.06 (-0.15, 0.26)		0.27 (0.04, 0.50)
≥ vs. <90th percentile (Odds ratio, 95% CI)	22/148	0.94 (0.44, 1.99)	13/151	0.89 (0.36, 2.22)	22/135	2.24 (1.05, 4.80)
S/D ratio						
Per SD (Beta, 95%CI)		-0.04 (-0.23, 0.15)		0.07 (-0.14 to 0.29)		0.24 (0.01, 0.48)
≥ vs. <90th percentile (Odds ratio, 95% CI)	19/151	0.93 (0.43, 2.05)	17/147	0.97 (0.43, 2.18)	21/136	2.96 (1.30, 6.73)
Presence of notching						
Unilateral (Odds ratio, 95% CI)	37/132	1.40 (0.77, 2.56)	38/124	1.38 (0.76, 2.50)	37/119	0.92 (0.50, 1.69)
Bilateral (Odds ratio, 95% CI)	80/89	0.90 (0.54, 1.50)	35/127	0.52 (0.28, 0.97)	42/114	1.21 (0.69, 2.13)

[a]Models adjusted for gestational weeks at visit, maternal age, pre-pregnancy BMI, infant sex, parity, marital status, payment for prenatal care, maternal smoking

[b]SAS warning: validity of model questionable, potential quasi-separation

Chapter 5. Public Health Importance

Although survival rates have dramatically improved due to advances in treatment and supportive care, childhood cancer survivors are at increased risk of secondary cancers, chronic disease, and functional impairments. The incidence of certain cancers (leukemia, non-Hodgkin lymphoma, testicular germ cell tumors) have increased from 0.7% to 1.2% per year, with the reasons for these increases largely unknown [101]. There are few known preventable causes of childhood cancers, thus the study of potential risk factors for childhood cancers is imperative. Due to evidence that childhood cancers may have a prenatal origin, various studies have examined perinatal characteristics such as birthweight, but studies on other prenatal factors are limited.

Our first study used a large population-based sample of California children to assess the impact of a number of maternal metabolic factors on childhood cancer risk. We found strong evidence for an increased risk of leukemia in offspring of diabetic mothers. Though our novel findings between maternal health conditions and rarer cancer types require further confirmation in the literature, our study nonetheless underlines the importance of prevention and management of these conditions during pregnancy. Our findings are especially relevant in California given its predominantly Hispanic population as Hispanic mothers are known to have some of the highest rates of obesity and diabetes [32, 41].

The high proportion of Hispanic women in our California population also afforded us the opportunity to examine whether childhood cancer disparities exist among the Hispanic population based on aspects of the neighborhood that the mother resided in during pregnancy. Since Hispanic foreign-born women have been shown to have better pregnancy outcomes than

their US-born counterparts, it is thought that Hispanic enclaves are supportive of the maintenance of positive health behaviors/beliefs of one's home country [74, 75, 134–136]. Overall, we did not find evidence that this protective advantage extends to the Hispanic women in our sample. In contrast, living outside of these enclaves was protective of some childhood cancers. To better interpret our findings, research on the distributions of risk and protective factors in these neighborhoods is needed. To date most studies have only examined their impact on birthweight or maternal smoking. The neighborhood environment has long been recognized as an important determinant of health, but it remains highly understudied in childhood cancer research, thus our work supports that it be taken into consideration in future research.

Although air pollution and smoking are associated with various pregnancy complications and negative birth outcomes the potential mechanisms linking these associations are not well understood [88, 89, 96]. Our third study examined the impact of these risk factors on placental vascular resistance, and found that both independently increase resistance. Since high resistance is itself predictive of the same negative health outcomes associated with these risk factors, these findings provide a potential biological explanation underlying these associations. Further study of the susceptible time windows during pregnancy would better elucidate the mechanisms at play as well as allow for better targeted interventions. Though smoking during pregnancy has declined, smoking prior to pregnancy remains high and the prevalence of smoking during pregnancy is likely underestimated.

Chapter 6. References

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