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Prenatal risk factors for childhood cancer and health: maternal diabetes, occupational physical activity and nativity

Author

Huang, Xiwen

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Prenatal risk factors for childhood cancer and health:

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A dissertation submitted in partial satisfaction of the

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by

Xiwen Huang

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ABSTRACT OF THE DISSERTATION

Prenatal risk factors for childhood cancer and health:
maternal diabetes, occupational physical activity and nativity

by

Xiwen Huang
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2022
Professor Beate R. Ritz, Chair

Protecting and improving the health outcomes of children is of fundamental importance. The first two studies of this dissertation focus on prenatal risk factors for childhood cancers. The first study includes cancer cases identified from the Danish Cancer Registry and diagnosed under 19 between 1977 and 2016. Controls were selected from Central Population Registry and matched to cases on sex and birth year. We also included cases ascertained from the Taiwanese Cancer Registry and all children born in Taiwan between 2004 and 2014 that are listed in the Maternal and Child Health database. With access to population-based registries in Denmark and Taiwan, we examined the association between maternal diabetes and childhood cancer risk. In Denmark, the risks of central nervous system tumors among children prenatally exposed to maternal type I diabetes were increased, particularly for glioma. In Taiwan, the risks of glioma were elevated among children whose mothers had gestational diabetes. There was a two-fold increased risk for hepatoblastoma.

Our second study includes cancer cases identified from the Danish Cancer Registry and diagnosed under 19 between 1968 and 2016 to investigate the effect of maternal occupational physical activity and childhood cancer risk. Overall, high levels of maternal occupational physical activity during pregnancy were associated with a higher risk of medulloblastoma with an indication of a dose-response pattern. Among health care professionals, maternal occupational physical activity exposures increased the risk of melanoma in offspring.

The distribution of adverse pregnancy, birth and subsequent child developmental outcomes in the U.S. is characterized by pronounced racial-ethnic disparities and maternal immigrant status. In the third study, we compared metabolic profiles generated by the liquid chromatography-high resolution mass spectrometry platform of newborns of foreign-born and US-born Hispanic women in California (1983-2011) in an untargeted manner. Dried blood spots of eligible healthy children were collected by the California Genetic Disease Screening Program. We found that differences in metabolic profiles exist between newborns of US-born and foreign-born Hispanic mothers with an indication of alterations in inflammatory and oxidative stress pathways which could not be explained by the measured demographic, health behaviors, gestational and environmental factors.

The dissertation of Xiwen Huang is approved.

Julia E. Heck

Roch A. Nianogo

Heather Christofk

Beate R. Ritz, Committee Chair

University of California, Los Angeles

2022

DEDICATION

This dissertation is dedicated to my parents, my family, my friends, and my mentors.

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LIST OF ABBREVIATIONS

13-HODE	13-hydroxy-9Z,11E-octadecadienoic acid
5-HTP	5-hydroxy-L-tryptophan
5-MIAA	5-methoxyindoleacetate
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BCBS	Blue Cross Blue Shield
CALINE4	CAlifornia LINE Source Dispersion Model
CNS	Central nervous system
CV	Coefficient of variation
CI	Confidence intervals
DSE-77	Danmarks Statistiks Erhvervsgrupperingskode
ELF-MF	Extremely low frequency magnetic fields
GDM	Gestational diabetes mellitus
HMO	Health Maintenance Organization
HR	Hazard ratios
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IDO	Indoleamine 2,3-dioxygenase

IGF-I	Insulin-like growth factor-1
JEM	Job exposure matrix
L-DOPA	3,4-Dihydroxy-L-phenylalanine
LTPA	Leisure time physical activity
LC-HRMS	Liquid chromatography with ultra-high resolution mass spectrometry
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphoma
NOCCA-DANJEM	An adaptation of Nordic Occupational Cancer Study – Job exposure matrix
NOCCA-JEM	Nordic Occupational Cancer Study – Job exposure matrix
OPA	Occupational physical activity
OR	Odds ratio
PL-SDA	Partial least squares discriminant analysis
PM2.5	Fine particulate matter, with diameters that are 2.5 micrometers and smaller.
Ref	Reference
SD	Standard deviation
SES	Socioeconomic status
VIP	Variable importance in the projection

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VITA

EDUCATION

2016	Master of Public Health, Epidemiology
	Columbia University in the City of New York
	New York, NY
2014	Bachelor of Science, Pharmacy
	Shanghai Jiaotong University
	Shanghai, China

PUBLICATIONS

Heck, J. E., Wu, C. K., **Huang, X.**, Chew, K. W., Tong, M., Federman, N., ... & Lee, P. C. (2021). Cohort study of familial viral hepatitis and risks of paediatric cancers. *International Journal of Epidemiology*.

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Chapter 1. Introduction and background

1.1 Childhood cancer overview

Even though childhood cancer is a rare disease, the incidence rates of childhood cancer have been slowly rising over the past few decades worldwide.[1] About 10,590 children in the U.S. under the age of 15 were diagnosed with cancer in 2018. Leukemia and central nervous system (CNS) tumors are among the most common childhood cancers in western countries.[2] The peak incidence of acute lymphoblastic leukemia (ALL) is between two and six years of age. The highest incidence of CNS tumors occurs through age 7. Embryonal tumors, including neuroblastoma, Wilms tumor, and retinoblastoma, mostly affect children under age 5. These observations implicate events prior to conception or during gestation in the genesis of the disease. Germline mutations are estimated to play a role in less than 10% of all pediatric cancer diagnoses. Prenatal exposure to radiation [3,4] and diethylstilbestrol [5] are established causes of childhood cancers but are relatively rare.

Childhood cancer incidence has been noted to vary by children's age, sex, and race/ethnicity. In the U.S., in children aged 0–4 years, leukemia was the most frequent cancer type, with CNS tumors being the second most frequent. However, lymphomas represented 22·5% of cases in those aged 15–19 years. Epithelial tumors and melanoma were the second most common tumor group in young people aged 15–19 years.[1] Incidence rates of childhood cancer, in general, are higher in boys than in girls, and the incidence sex ratio depends on age group, regions, cancer subtypes, and race/ethnicity, with the highest being reported in South Asia in the age group of 5–9 years (incidence sex ratio=1.7). While white children have the highest incidence in most of the cancer types (e.g., lymphoma, CNS tumors, neuroblastoma, retinoblastoma, renal tumors, hepatic

tumors, malignant bone tumors, germ cell tumors), Hispanic children are 10% higher in the incidence of ALL compared to white children.[1]

1.2 Prenatal risk factors

1.2.1 Maternal diabetes

Gestational diabetes mellitus

The prevalence of gestational diabetes mellitus (GDM) varies from 1% to 16%, depending on diagnostic criteria and the study population.[6] In the U.S., about 6% - 9% of pregnant women develop GDM. The incidence of diabetes during pregnancy has increased in recent years from 4.6% in 2006 to 8.2% in 2016.[7] In Los Angeles County, a hospital record based study reported the age-adjusted prevalence of GDM increased from 1.45% in 1991 to 4.79% in 2003, with the highest increase in annual rate among Hispanics (9.9%).[8] The increase in the incidence of GDM was more evident among women who had low income, were overweight, were aged between 45-64 years, and had insufficient physical activity.[7]

In European countries, prevalence estimates of GDM are on average between 2% to 6%, with a lower estimate (mostly <4%) in Denmark, Sweden, and the United Kingdom compared with southern Europe or Mediterranean countries (mostly >6%).[9] The implementation of universal screening procedures tends to find a higher prevalence of GDM. A prospective cohort study on an island in Italy reported the prevalence of GDM was 22.3% [10], and a nationwide study in Germany estimated the overall prevalence of GDM was 13.2%.[11] However, Denmark has a tradition of only screening risk groups for the past two decades. A Danish prospective cohort study in which diagnostic testing with a 2-hour oral glucose tolerance test was offered to all

participants (N = 5,235) reported a prevalence of 2.4% in 2000 and concluded that selective screening and diagnostic procedures in Denmark should have comparable sensitivity to a universal screening program.[12] Although diagnostic procedures in Denmark are not uniform, a validation study of GDM diagnosis recorded in the Denmark National Patient Register reported that the registry data alone was capable of identifying 76% of pregnancies with GDM diagnosis confirmed by a detailed review of hospital records.[13]

Several risk factors for GDM have been well established, including nonwhite ethnicity, obesity, previous history of GDM, advanced maternal age, and family history of diabetes [11,14-16] while no concrete conclusion can be drawn as to the effect of cigarette smoking,[17] dietary factors or leisure time physical activity on the risk of GDM due to the variation in exposure measurement, availability of data and power limitations.[18] The incidence of diabetes in pregnancy varies by race and ethnicity. Black and Hispanic women have higher rates of pre-gestational diabetes and Asian and Hispanic women have higher rates of gestational diabetes.[19] Other risk factors for GDM, including maternal age and obesity, are of particular interest for this proposal because of putative associations with childhood cancers in offspring.[20-22]

The health consequences for children whose mothers had GDM are only partly known, although both short-term and long-term effects have been reported. Increased risks of perinatal mortality, stillbirth, congenital anomaly, macrosomia, shoulder dystocia, neonatal hypoglycemia, obesity, and of developing type 2 diabetes have been observed consistently in large cohort studies.[23]

Several pathophysiologic pathways of GDM have been proposed.[24] Pregnancy-associated hormones, including estrogen, androgen, progesterone and cortisol, are suggested to be related to the etiology of GDM because the levels of these hormones increase during pregnancy but drop after delivery, and so does GDM. Previous it has been reported that cord blood estradiol in the GDM group was substantially lower.[25] As a potential mechanism it has been proposed that estrogen may enhance the adaption process to high insulin demand during pregnancy by acting directly on β–cell mass to increase insulin biosynthesis.[26] GDM may develop if this adaption process is not efficient, suggesting that a high level of estrogen may protect women from GDM. Abnormal increase in androgens has also been associated with GDM [27,28] probably because of its role in inducing insulin resistance and reducing glucose uptake in adipose and muscle tissues in women.[29] Adipose tissue is also suggested to cause GDM because it produces adipocytokines which were related to the changes in insulin sensitivity in pregnant women.[30] Since previous studies reported that steroid hormones (i.e., androgen), maternal use of exogenous hormones (oral contraceptives, fertility drugs, etc.) and pre-pregnancy BMI increase the risk of ALL, CNS and germ cell tumors,[31-34] there is a convergence of etiological hypotheses for maternal diabetes and childhood cancer.

Pre-gestational diabetes in pregnant women

In the U.S., about 1% -2% of pregnant women have pre-gestational diabetes. Recent studies indicated that the percentage of pre-gestational diabetes increases with obesity. A cohort study reported an increase in the prevalence of pre-gestational diabetes in Northern California from 0.58% in 1996 to 1.06% in 2014. Increases occurred in all race and ethnicity groups, with the largest observed among Hispanic women.[35] A population-based cohort study in Canada reported

that the incidence of pre-gestational diabetes and GDM doubled in the past fourteen years.[23] Moreover, a cohort study in the UK reported that the percentages of type I and type II diabetes among pregnant women more than doubled between 1995 and 2012, from 1.56 to 4.09 per 1000 pregnancies and from 2.34 to 10.62 per 1000 pregnancies, respectively. The study also found that pregnant women with pre-gestational diabetes were older and had higher BMI.[36] In Denmark, 1.7% of pregnant women (N = 71,304) had type I diabetes between 1993 and 1999.[37] The change in the incidence of pre-gestational diabetes has not been reported for pregnant women specifically. Considering that the number of Danes with diabetes has more than doubled from 2000 to 2016 and women make up 44% of all diabetes diagnoses, it is reasonable to expect an increasing trend in pre-gestational diabetes among pregnant women. Adverse pregnancy outcomes are reported with pre-gestational diabetes, including perinatal mortality, congenital malformations, cesarean section, macrosomia, stillbirth and preterm delivery of the offspring.[37]

Maternal diabetes and childhood cancers

A registry-based case-control study in Washington State where cases were retrieved from the cancer registry from 1980-2004 and matched with ten controls by birth year reported that the crude odds ratio of neuroblastoma was 1.71 (95% CI: 0.91–3.22) for all types of maternal diabetes and 1.84 (95% CI: 0.98–3.47) for GDM particularly. The association with GDM was stronger for neuroblastoma diagnosed at age <1 year (OR= 2.82, 95% CI: 1.24–6.39) and with distant metastases (OR=2.53, 95% CI: 1.17–5.44) compared with cases diagnosed after one year and with local tumor spread.[38] It was suggested that clinical heterogeneity of neuroblastoma might explain the difference in the strength of the effect. Diagnosis of neuroblastoma at an age

younger than one year is associated with better prognosis and less aggressive treatment, particularly stage 4s which has the highest rate of spontaneous regression of any cancer.

A case-control study from the California Cancer Registry with 11,149 cancers cases diagnosed before age six between 1988 and 2013 reported an increased risk of Wilms tumor (OR=1.45, 95% CI: 0.97-2.18) in children of mothers with pre-gestational diabetes. Higher risks of brain tumors, hepatoblastoma, neuroblastoma, retinoblastoma and Wilms tumor were observed among children of mothers with GDM, with the odds ratio ranging between 1.14 for Wilms tumor to 1.49 for hepatoblastoma. The confidence intervals for the cancer types were too wide to draw conclusions probably because of the underreporting of GDM recorded on the birth records and limited sample size, with the percentage of pre-gestational diabetes and GDM being 1.6% and 3.2% among controls, respectively.[34]

A cohort of over 53, 000 children born to more than 36,000 parents diagnosed with autoimmune disease were followed up for cancer incidence in Denmark during 1968–1993.[39] Type I diabetes accounted for 23.6% of all autoimmune diseases identified in the study. In the study, all four lymphoma cases had parents with diabetes of any types and the risk for lymphoma (standardized incidence ratios =1.30, 95% CI: 1.0–2.4) was elevated compared to the national childhood cancer incidence rates stratified by sex, age groups and calendar periods.

Interestingly, Westbom et al. [40] reported that the odds ratio of childhood cancers in children from mothers with pre-gestational diabetes (N=10 exposed cases) was 2.25 (95% CI: 1.22–4.15) with adjustment of year of birth, maternal age, parity, multiple births, and birth weight while an

increase in the risk of cancer was not observed among children whose mothers had other autoimmune diseases including systemic lupus erythematosus, rheumatic arthritis, scleroderma, Crohn's disease or ulcerative colitis, multiple sclerosis, and thyroiditis. These results were based on the linkage of the Swedish Medical Birth Registry and the Cancer Registry between 1987 and 1997. However, the study population was restricted to children alive at the age of one, which can lead to a collider (selection) bias and potentially attenuate the observed effect estimate as both maternal diabetes and childhood cancer increase infant death rates.[41,42] Adjustment for birth weight didn't remove the increase. The conclusion from the article that the effect estimate of maternal diabetes is not fully explained by birth weight may not be valid as adjusting for birth weight - which is in the causal path between maternal diabetes and childhood cancer risk - may have also induced collider bias. But the registry data records over 98% births and diagnosis of pre-gestational diabetes in Sweden during that period, thus the effect estimate for maternal diabetes on the risk of childhood cancer is informative.

Seppälä et al. [43] analyzed a total of 2,029 cases diagnosed by age 20 from the Finnish cancer registry between the years 1996–2014 and matched 10,103 population controls by birth year and sex. The crude OR for any childhood cancer was 1.32 (95% CI: 1.14–1.54) in the offspring of mothers with chronic or gestational diabetes compared to the offspring of the nondiabetic mothers. With adjustment of maternal age, parity and smoking status, the risk remained elevated (OR=1.28, 95% CI: 1.10–1.50). When examining the effect on each cancer type, there was an increase in the risk of CNS tumors (OR=1.23, 95% CI: 0.89-1.69). Pre-gestational diabetes seemed to have a stronger effect estimate on the risk of CNS tumors. About 1.5% of cases and 1.6% of controls took antidiabetic medications (i.e., insulin, metformin, or both) during

pregnancy. Of note is that the percentage of GDM was much higher than pre-gestational diabetes (10.4% vs. 1.4% in cases and 8.0% vs. 1.3% in controls). Their results suggest that antidiabetic medications during pregnancy may reduce the risk for childhood cancer (adjusted OR=0.83, 95% CI: 0.36–1.94), especially for gestational diabetes (adjusted OR= 0.26, 95% CI: 0.05–1.25).

There is one paper published using the Danish population, which will thus have overlap with the proposed study, however this paper aimed to examine a number of adverse childhood outcomes; while it reported on neoplasms in children, it grouped all cancers together, making it distinct from our study goals. This population-based cohort study used all singleton births born in Denmark between 1977 and 2008 (N=1,781,576) and identified 7253 cancer cases diagnosed before 30 years of age to study long-term health effects in the offspring of mothers with different types of diabetes.[44] An increased risk of any childhood cancer was found in children whose mother had pre-gestational type I diabetes [adjusted hazard ratio (HR)= 1.3, 95% CI: 0.5–3.5], type II diabetes (adjusted HR=2.2, 95% CI: 1.5–3.2) but not GDM (adjusted HR=0.7, 95% CI: 0.4–1.3). The authors stratified the analysis by maternal and paternal diabetes and didn't find an increased risk of childhood cancer prenatally exposed to paternal diabetes of any type (adjusted HR= 1.0, 95% CI: 0.7–1.5). The results indicated that the change in the intrauterine environment caused by maternal diabetes might play a role in the etiology of childhood cancer. This study utilized some of the same cases to be included in the present study, however the proposed study will be different in several ways. The authors did not report stratified effect estimates for each cancer type, even though previous studies showed that maternal diabetes affected cancers differently. Further, the use of antidiabetic medication during pregnancy was not considered in the analysis, which calls for a further examination of the effect of maternal diabetes on the risk of

childhood cancer in these data. Finally, the present case-control study (N = 2,160 cancer cases, 2,076,877 non-cases) will also add five additional years of cancer data and include cases diagnosed only before 20 years of age.

1.2.2 Maternal occupational physical activity

Although previous studies suggested that maternal leisure-time physical activity (LTPA) during pregnancy has beneficial health outcomes for mothers and offspring,[45-48] studies have reported that a high level of maternal occupational physical activity (OPA) including physically demanding work, prolonged standing and walking, lifting and carrying, shift and night work, and high cumulative work fatigue was associated with adverse birth outcomes including fetal death, preterm birth and low birthweight.[49-55] The effect on fetal growth and size at birth is dependent on the type, intensity, frequency, duration and the timing of the exercise when performed.[56]

In Denmark, all women are entitled to 4 weeks of prenatal maternity leave, and the majority of women are entitled to either a maternity leave benefit or even their full wage during prenatal leave if women have been on the Danish labor market for at least 13 weeks and have worked for at least 120 hours. The amount of allowance depends on how much women work and the agreement with employers. Recent figures show that pregnant women in Denmark are absent from the labor market for 48 working days, which includes the 4 weeks of pre-birth leave (Danish Ministry of Employment, 2010). Nearly 18% of women answer that they have experienced more favorable working conditions (e.g., fewer tasks, reduced number of shifts and working hours, etc.) before maternity leave. Women who experience pregnancy complications

or who work in a condition that might put the baby at risk are entitled legally to be absent from work prior to their 4-week maternity leave.[57] If women with high-risk pregnancies are granted leaves earlier in pregnancy, then levels of exposure to OPA in the population of pregnant women will be lower. This could attenuate any observable effects in our study.[58]

Maternal occupations and childhood cancers

To our knowledge, no published studies have examined the effect of either maternal LPTA or OPA during pregnancy on childhood cancer risks. Yet, prior studies which focused on job titles have indicated that occupations requiring a lot of standing, walking or dynamic movement are related to higher risk of childhood cancer, especially brain tumors, including studies of agricultural activities,[59-63] motor vehicle related activities,[63,64] hairdressers,[65] sales,[66] leather/metal workers,[67] teachers,[60] childcare workers,[68] nurses and other health care workers (e.g., physicians, dentists, dental assistants, veterinarians and pharmacists),[65,68] laundry owners,[68] sewing machine operators,[69] textile industry workers.[59,67]

A population-based case-control study coordinated by IARC used cases of childhood brain tumors from seven countries (N=1,218 cases) to examine the effect of individual occupation on the risk of childhood brain tumors [59] and found that several associations consistent with previous results: agricultural work,[61-63] motor vehicle occupations [63,64] and electrical work for both fathers and mothers. A higher risk of astrocytoma among child was suggested for mothers working as nurses (OR=2.2, 95% CI: 0.7-8.1), and also in hairdressers (OR=2.5, 95% CI: 0.2-18.0) before conception and OR=1.5 (95% CI: 0.4-26.2) during pregnancy. Children whose mother worked as a teacher during pregnancy experienced 1.8 times (95% CI: 0.6-6.0) the risk of astrocytoma

compared to those never employed as a teacher,[66] but this analysis was not adjusted for other covariates.

The maternal occupations which were found more frequently among all childhood cancer cases combined than in controls in Finland during the period 1959-75 included farmers' wives, pharmacists, saleswomen, bakers, and factory workers of an unspecified nature.[63]

In a case-control study from Canada, based on job titles, a twofold risk increase was observed for astroglial tumors (OR = 2.3, 95% CI: 0.8–6.3) and for all childhood brain tumors (OR = 2.3, 95% CI: 1.0–5.4) among sewing machine operators with the hypothesis that maternal occupational exposure to extremely low-frequency magnetic fields (ELF-MF) shortly before and during pregnancy increase the incidence of childhood brain tumors.[69] A case-control study carried out in five provinces in Spain (N= 128 cases) where employment history was collected through interviews found that children of mothers working at home had a seven times risk increase (OR = 7.0, 95% CI: 1.59-30.79) of developing acute lymphoblastic leukemia (ALL). The majority of women worked from home sewing different types of tissues (i.e., cotton, wool, synthetic fibers).[70] Additionally, maternal employment in the textile industry increased the risk of childhood brain tumors.[59]

There are limited studies on maternal occupational exposures in relation to medulloblastoma. Self-reported occupational exposures to chemicals from 1 year before conception to lactation increased the risk of brain tumors and the increase could not be explained by paternal exposure to solvents.[71] In contrast, a pooled analysis based on three population-based case-control studies

in Europe found no association between maternal exposures to polycyclic aromatic hydrocarbons, diesel motor exhaust, asbestos, silica, metals and the risk of embryonal CNS tumors around the time of conception or diagnosis.[72] Together, results are mixed for associations with occupational chemical exposures and changes in pathologic classifications makes it difficult to compare to previous studies. Several maternal occupations with potentially high OPA increased the risk of medulloblastoma, including pig and chicken farming, employment as an electrician, and employment in agriculture.[59,62] Each of these maternal occupations also appeared in the job exposure matrix (JEM) of OPA applied in the present study.

The results suggest a moderate to high risk of childhood cancers among women in a group of occupations that require prolonged standing and walking, lifting and carrying, shift and night work, or high cumulative work fatigue, but with limited sample size and control for potential confounders, the estimates may be unstable and prone to residual confounding. We are aware that some of the occupations with OPA exposure are highly correlated with certain carcinogens like pesticides in agricultural activities and hair dyes in hairdressers. With the Denmark JEM developed for cancer research specifically, we can identify 28 chemical agents which can be adjusted for in the analysis when appropriate. Note that the previous results of studying the effect of paternal occupations and childhood cancers depend on the sources of employment data (e.g., birth certificates, self-report, interviews), the methods of exposure assessment (e.g., the construction of job exposure matrix, duration of employment and employment history, information on use of protection equipment), the definition of exposure period, capacity of confounding control, sample size, control selection, etc. which can lead to variation in the estimates.

1.2.3 Maternal nativity

Although Hispanics share many common cultural characteristics, research has documented that the demographics, health behaviors, income, family characteristics, language used at home, and availability of health care of the foreign-born Hispanics varied by their birth country. Despite disparities in health care access and socioeconomic status, previous research consistently reported the risks of infant mortality, low birth weight and preterm birth among foreign-born Hispanic women are lower than their US-born counterparts at local levels and nationwide. However, the risk of miscarriage and birth defects varied between foreign-born and US-born Hispanic mothers in a less consistent manner.[73]

Based on nationwide samples between 1983 and 1984, the infant mortality risks were lower among Hispanic infants whose mothers were born outside the U.S.[74] Powell-Griner proposed that misidentification of the identity of foreign-born mothers as residents and reliance on midwives in regards to infant mortality reporting might explain the underreporting of infant death observed in the Hispanic surname population in Texas.[75]

Hispanic infants of foreign-born were less likely to have low birth weight than were Hispanic infants of US-born mothers in nationwide samples.[73,74,76] Similar disparities in birth outcomes between maternal nativity groups were consistently reported in regional samples. In a California study, foreign-born Latina women were less likely to have low birth weight infants than US-born Latinas, while no difference in the likelihood of low birth weight infants was observed between foreign- and US-born Asian, black, or white women.[77] A study based in Chicago reported that

immigrant Mexican women had a significantly lower risk of low birth weight and preterm births and factors including maternal age, marital status, maternal education, use of prenatal care, parity, infant's sex, and the maternal residence census tract could not explain the health advantages of infants of foreign-born mothers.[78] A similar trend was reported in New York City where the risk of preterm birth was lower in foreign-born women than US-born women while the socioeconomic status was improved in US-born women.[79] Likewise, a recent study from the New York City found similar evidence of the immigrant health paradox across racial/ethnic groups (i.e., Asian, non-Latina white, non-Latina black, Puerto Rican and all other Hispanic) for preterm birth and low birth weight.[80] In Utah, infants of foreign-born Hispanic mothers had lower risks of adverse birth outcomes, including low birth weight, preterm birth and small-for-gestational-age, which is consistent with the findings in the nationwide and regional samples.[81] In Texas, Mexican immigrant mothers had the lowest risks of low birth weight and preterm babies and authors suggested that marital status at birth could explain a small amount of variance.[82] A meta-analysis where studies published before the 90s were synthesized reported similar results that in spite of adverse socioeconomics and demographic profile, foreign-born Mexico mothers had a lower risk of low birth weight, preterm birth and infant death in comparison to US-born Mexicans with an improved sociodemographic profile (including maternal age, maternal education, initiation of prenatal care).[83] In a review study where country origin was taken into account, infants whose mother was born in Puerto Rico had higher risks of low birth weight compared to their US-born counterparts.[84] It is likely that the unmeasured environmental and behavioral factors, rather than the low socioeconomic status itself, had protective effects against adverse birth outcomes among foreign-born Hispanic mothers.

Among immigrant women in Chicago and Milwaukee, a dose-response was observed as the longer the time immigrant women stayed in the U.S. less likely they had favorable birth outcomes (favorable birth outcomes if the infant does not have any of low birth weight, preterm or intrauterine growth restriction) controlling for social, behavioral, environmental and medical factors.[85]

With regards to risks of cancer, Menck et al. reported differential cancer risks are seen between foreign-born and US-born Hispanic adults.[86] For childhood cancers, Heck et al. found that the lowest risk of gliomas, astrocytoma, neuroblastoma, and nephroblastoma was among the children of foreign-born Hispanic mothers compared to non-Hispanic White with the risk estimates for children of US-born Hispanic mothers fell between. Further studies on environmental and behavioral factors are warranted to explain the Hispanic epidemiologic paradox in childhood cancer. Understanding protective factors in these populations can inform interventions to reduce reproductive health disparities among all Americans.

Potential explanations of the immigrant paradox

Several mediators (i.e., behavioral, medical, nutritional, cultural or environmental factors) were proposed to explain perinatal advantage of foreign-born Hispanic women, but these explanations for Hispanic health paradoxes have not been sufficiently tested due to the interplay of conceptual and data limitations. With metabolomics data, we expect to identify potential biomarkers of maternal behaviors and social and physical environments, acculturation or stress experienced by women during pregnancy in children's dried blood spots. Moving forward, the potential biomarkers from metabolomics in children facilitate a greater understanding of the specific

physiological pathways through which maternal socioeconomic, demographic, and psychosocial factors shape health in offspring.

Healthy immigrant selection is among the possible explanations where self-selected immigrants are on average healthier than the native-born in the destination countries.[87] In this study, we are not able to examine whether such health advantages extend to the offspring for lack of samples of women who remain in their home country.

Health behaviors (i.e., dietary habits, smoking, breastfeeding, length of inter-pregnancy intervals) were suggested on the causal pathway between maternal nativity and health in offspring. With regards to dietary patterns, a cross-sectional study reported that U.S. natives consumed substantially more omega-3 fatty acids than immigrants (2.45 g vs. 1.55 g) based on a self-reported food frequency questionnaire.[88] Balcazar et al. [89] noted that acculturation and education levels were highly correlated with the type of food intake among Hispanic women in the US Hispanic Health and Nutrition Examination Survey. Lower acculturated, lower educated women consumed foods cooked in lard, beans and legumes more frequently. In contrast, higher acculturated and higher educated women ate raw vegetables and white meat more frequently. In a study using the National Health and Nutrition Examination Survey (NHANES) data (1999–2004) and 24-h dietary recall administered by trained interviewers examined the effect of birthplace on dietary patterns in Hispanic adults (n= 3,375 Mexican, n=622 other Hispanic), being born in the US was associated with a lower percentage of energy from legumes, beans, high-fat milk, fruits, and vegetables but with a higher percentage of energy from non-Mexican fast food in Mexican and other Hispanic groups.[90] More foreign-born than US-born Hispanics

reported consuming legumes and fruits per day, respectively. In contrast, 10.8% more US-born than foreign-born Hispanics consumed non-Mexican fast food. A substantial difference in dietary patterns was observed between Spanish and non-Spanish speakers, which were used as an indicator of acculturation. Although the study lacked data on the level of acculturation and the sample size was too small to further stratify for ethnicity in other Hispanic groups, the results derived from these national representative samples and comprehensive dietary information indicated a clear relation between birthplace and eating habits. The results are consistent with the observation that foreign-born Latina women were observed to consume more nutritious diets than their US-born counterparts.[91] Variations in food intake patterns have been observed within Hispanic populations in the US, where the majority (80.6%) was foreign-born. Cubans (n = 2,128) had higher energy and alcohol intake while Mexicans (n = 5,371) had higher consumption of vitamin C, calcium, and fiber. Dominicans (n = 1,217) had the lowest intakes of total energy, macronutrients, folate, iron, and calcium and Puerto Ricans (n = 2,176) had the lowest vitamin C and fiber intakes.[92]

In terms of smoking, higher acculturated women have a higher prevalence of cigarette smoking among middle-aged Mexican American women.[89] The categories of acculturation (i.e., low acculturated, bicultural, high acculturated) were based on the General Acculturation Index collected by trained interviewers. Questions included language skills, the country where the subject spent early life, race/ethnicity and birthplace of friends and their attitudes towards having a Hispanic background. The measure of acculturation was strongly correlated with maternal nativity.

Other health behaviors of interest to explain the Hispanic Paradox in terms of health in offspring is breastfeeding practices. Foreign-born Latinas were more likely to initiate and continue breastfeeding compared with US-born Latinas.[93] Furthermore, foreign-born mothers are more likely to live less than 500 meters from primary highways or roads [94], which increases the possibility of being exposed to vehicle exhaust.

Stronger social ties and support have been hypothesized to be related to reproductive health advantages among immigrants,[73,95,96] however, studies did not have access to such information to test the hypothesis. Evidence indicated that the effect of social ties on birth outcomes varied by nativity. Higher exposure to ethnic enclaves was associated with lower birthweight among infants of US-born mothers of Mexican origins but not among infants of Mexican immigrants after adjusting for a range of individual-level factors, including prenatal care, marital status, age, education, and parity.[97] A number of studies have also indicated that social relationships can have both positive and negative impacts on immune function [98] which in turn affect the health of offspring. Epigenetic studies have demonstrated the direct effect on DNA function of the social environment. Moreover, it may exert biological influences through changes in epigenetic across generations.[99-101]

Besides, maternal health complications are potential explanations for such health disparities. Compared to health behaviors and social environment during pregnancy, maternal health complications are more consistently recorded and widely available for the purpose of research.

Biomarkers of nativity in Hispanic women

Inflammatory biomarkers have been linked to acculturation status in non-pregnant adult Hispanic women.[102,103] A downregulation of inflammatory responses was reported by previous studies using different sets of inflammatory biomarkers. A study analyzed serum samples of non-pregnant Mexico-born women of reproductive age and observed an increase in high levels of C-reactive protein (3.01–10.00 mg/L defined based on cardiometabolic risk) with increasing acculturation levels in these women.[103] A study focused on older individuals (40 years+) also found foreign-born Hispanics to have lower levels of inflammatory markers (i.e., C-reactive protein and fibrinogen) compared to their US-born counterparts after controlling for socioeconomic status, health behaviors and access to care.[102]

Chapter 2. Maternal diabetes and childhood cancer risks in offspring: two population-based studies

2.1 Abstract

The effects of maternal diabetes on childhood cancer have not been widely studied. We examined the effects in two population-based studies in Denmark (N = 6,420 cancer cases, 160,484 controls) and Taiwan (N = 2,160 cancer cases, 2,076,877 non-cases) using logistic regression and Cox proportional hazard regression adjusted for birth year, child's sex, maternal age and birth order. In Denmark, the risks of central nervous system tumors among children prenatally exposed to maternal type I diabetes were increased (OR= 2.44, 95% CI: 1.40-4.24), particularly for glioma (OR= 2.33, 95% CI: 1.04-5.22). In Taiwan, the risks of glioma (HR= 1.59, 95% CI: 1.01-2.50) were elevated among children whose mothers had gestational diabetes. There was a two-fold increased risk for hepatoblastoma (HR= 2.02, 95% CI: 1.02-4.00). Our results suggest that maternal diabetes are important risk factors for childhood cancer, emphasizing the need for effective interventions targeting maternal diabetes to prevent serious health effects in offspring.

2.2 Introduction

Childhood cancer is a rare disease, but the incidence rates have been slowly rising over the past few decades worldwide.[104] Leukemia and central nervous system (CNS) tumors are among the most common childhood cancers in the developed countries.[2] The incidence of several childhood cancer types peaks in early life and infancy, implicating events prior to conception or during gestation in the genesis of the disease. However, germline mutations are estimated to play a role in less than 10% of all pediatric cancer diagnoses.[105] Prenatal exposure to radiation [106] and diethylstilbestrol [5] are established causes of childhood cancers but are relatively rare.

Women of childbearing age are at increased risk of type I, type II, and gestational diabetes internationally,[107,108] driven in part by the increasing prevalence of obesity among pregnant women.[109] In pregnancy, diabetes promotes fetal growth and increase the expression of proinflammatory cytokines in the placenta, presenting possible biologic mechanisms linking these disorders to childhood cancers.[110-112] However, the impact of maternal diabetes on childhood cancer risk has not been extensively studied. A higher risk of leukemia has previously been associated with all types of maternal diabetes.[22,34,43,113] One study differentiated between type I and type II diabetes and reported that maternal type I diabetes but not type II diabetes was associated with a higher risk of leukemia in offspring.[113] Results for other types of childhood cancer have been inconsistent.[34,43,113-118]

Maternal gestational diabetes has been known to be related to race/ethnicity, with non-Hispanic whites having the lowest risk and Asians having the highest risk.[119] Studies in the U.S. have

consistently demonstrated that women from racial and ethnic minority groups (i.e., Native American, Hispanic, Asian, Black) are more likely to have type I or type II diabetes than are non-Hispanic white women.[108,120] Using two population-based registries in Denmark and Taiwan, we aimed to examine the contributions of different types of maternal diabetes to the risks of childhood cancers. With access to nationwide registries in Denmark and Taiwan, we were able to investigate the risks of childhood cancers in these populations with distinctly different underlying distributions of maternal diabetes and childhood cancer types. A previous cohort study in Denmark reported increased risks of acute lymphoblastic leukemia (ALL) (age <15) among offspring of mothers with pregestational and gestational diabetes during the birth years 1996–2015.[121] Here, we expand the study period back in time (1977-2013) and look across other cancer types up to the age of 19 following exposure to maternal diabetes in utero.

2.3 Methods

Denmark

We included all cancer cases born in Denmark between 1977 and 2013, aged 0–19 at diagnosis, and diagnosed between 1977 and 2016. Controls, randomly selected from the Central Population Registry,[122] were frequency matched by birth year and sex (ratio 1:25) and free of cancer at the date of diagnosis of the corresponding case. Children who were likely not viable (gestational age ≤ 20 weeks or birth weight < 500g, n = 17) were excluded, resulting in 6,420 cases and 160,484 controls for the final analyses. This case-control data set has been used previously to study the risk of childhood cancers from occupational and perinatal factors.[123-127] The cases and controls were linked to the Medical Births Registry [128] and Danish National Patient Registry [129] based on

their unique Central Person number assigned at birth. This 10-digit number includes information on date of birth and sex.

Childhood cancer cases were identified from the Danish Cancer Registry that contains information on the Central Person number, morphology, topography, and date of diagnosis, among other factors.[130] The diagnosis was based on the International Classification of Diseases (ICD-O) until 2003 and the International Classification of Diseases, Revision 10 (ICD-10) thereafter; the subtype of cancer was based on morphology recorded in the International Classification of Childhood Cancer (ICCC) revision one until 2003 and revision three thereafter.[104,131] For CNS tumors, we included both malignant and benign tumors identified by the last digit of the morphology code (i.e., -3 is for malignant, -0 or -1 is for benign). Astrocytoma, the main subtype of gliomas, was reported separately if the effect estimates were different from the results of gliomas overall.

Information on maternal diabetes diagnoses was retrieved from the Danish National Patient Registry (1977-2016) and the Medical Births Registry (1977-2013) using International Classification of Disease codes (ICD-8 codes during 1970-1993 and ICD-10 codes since 1994). Type I diabetes and type II diabetes were identified for mothers who had received an ICD-8/10 code of diabetes (Supplemental Table 1) before childbirth. Type I and type II diabetes were defined as a diagnosis before childbirth rather than before pregnancy because preexisting but undiagnosed diabetes is likely to be registered during pregnancy, in accordance with previous studies of maternal diabetes in Denmark.[44,132] Because type I or type II diabetes were recorded

using the same code (ICD-8: 250) between 1977 and 1986, the below criterium were used to differentiate between type I and type II diabetes during that period:[132-134] a specific code of type I or type II diabetes registered later or age at diagnosis of diabetes (type I: < 30 years and type II: ≥ 30 years). If a mother was diagnosed with both types before the index childbirth (n=100, 5.1% of diabetes cases), she was classified according to the type that was first diagnosed. Gestational diabetes was identified for mothers who did not have a diagnosis of type I or type II diabetes and had received a diagnosis of gestational diabetes during the index pregnancy (Supplemental Table 1).[133]

Multivariable unconditional logistic regression analyses were used to estimate associations with maternal diabetes and childhood cancer in offspring. All models were adjusted for matching variables, birth year, and child's sex. We utilized unconditional logistic regression, breaking the matching, to improve statistical power.[135] The selection of additional covariates was based upon the literature, and we applied the change-in-estimate-criterium (included covariates that changed estimates by 10% or more). For maternal diabetes, we identified potential confounders from previous studies [34,43,113] (i.e., maternal age, birth order). We also considered adjustment for other covariates, including paternal age, maternal socioeconomic status, maternal smoking at the first prenatal visit (ever vs. never), maternal birthplace (i.e., Denmark, Europe, other), and maternal infections during pregnancy, but adjustment for these factors did not change point estimates by more than 10%. Therefore, final models adjusted for birth year, child's sex, maternal age, and birth order. Birth weight, gestational age, or presence of congenital anomalies were not adjusted as we consider these factors to be on the causal pathway, and adjustment for them may cause collider stratification bias.[136] Because it has been suggested that age at diagnosis modifies the

effect estimate of maternal diabetes on childhood cancer risk, we additionally examined the associations stratified by age at diagnosis of the offspring (0-14, 15-19 years) for CNS tumors; this also allowed us to compare our results to previous studies.[113]

In a sensitivity analysis of the possible cancer risks following maternal diabetes, we additionally adjusted for covariates which were only available for a subset of the overall sample (i.e., maternal smoking during pregnancy (available since 1991), maternal pre-pregnancy BMI (available since 2003). All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sample sizes were predetermined by the number of cancers in Denmark. According to our power calculations, a study with the number of cases and controls we selected will allow us to detect an odds ratio for childhood cancer of 1.5 or more in those prenatally exposed to maternal diabetes compared to those prenatally unexposed to maternal diabetes, at an exposure prevalence of 0.3% in population controls (power= 80%, two-sided p-value=0.05).

Taiwan

The data we relied on has been previously described.[137] In brief, cases were ascertained from the Taiwanese Cancer Registry. Maternal diabetes status recorded as ICD-9 (Supplemental Table 2.1) was acquired through linkage to the National Health Insurance Research Database provided by the Health and Welfare Data Science Center in Taiwan. The current analysis includes 2,160

cancer cases, aged 0-11 at diagnosis between 2004-2014 and 2,076,877 non-cases born between 2004-2014.

We estimated the associations between maternal diabetes and risks of pediatric cancer types using Cox proportional hazard models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Following the same strategy as in the Danish analyses, we adjusted for the child's birth year, sex, maternal age, and parity in the final model.

2.4 Results

Denmark

Demographic and gestational characteristics were similar among cases and controls (Table S2.2). Mothers with diabetes tended to be older, less likely to report smoking, and more likely to be born outside of Europe, and the children of diabetic mothers had, as expected, higher birth weight and birth order (Table S2.3).

Overall, we observed an increase in the risk of childhood cancers combined in children whose mother had type I or type II diabetes, but no increase was observed for gestational diabetes. While the point estimates for ALL in offspring were clearly above one for maternal type I diabetes (OR=1.44, 95% CI: 0.64, 3.23) and gestational diabetes (OR=1.38, 95% CI: 0.77, 2.45), the confidence intervals were wide and included the null value. For CNS tumors, we observed a positive association with type I diabetes (OR = 2.44, 95% CI: 1.40-4.24), while there was no association with gestational diabetes (Table 2.1). Children prenatally exposed to type I diabetes

had a higher risk of malignant CNS tumors (7 exposed cases, OR = 2.18, 95% CI: 1.04-4.62) and benign CNS tumors (6 exposed cases, OR = 2.81, 95% CI: 1.25-6.31). Gliomas were positively associated (OR = 2.33, 95% CI: 1.04-5.22) with offspring prenatal exposure to maternal type I diabetes, and the association was stronger for astrocytoma (6 exposed cases, OR=3.61, 95% CI: 1.61-8.11). For type II diabetes, the risk of all childhood cancers combined was increased by 64% (95% CI: 0.97-2.77). However, due to the limited sample size, we were not able to examine associations with specific types of cancer.

We observed that the estimated effect of maternal type I diabetes on the risk of CNS tumors in offspring varied by age at diagnosis, with diagnosis age 15-19 being most strongly associated with CNS tumors (Table 2.2).

Sensitivity analyses with additional adjustment for maternal smoking and pre-pregnancy BMI for diabetes yielded largely similar results as the main findings (Table S2.4, Table S2.5).

Taiwan

Cancer cases were more likely born in earlier years with low or high birth weight, in families with lower income and younger parental age, and with higher birth order (Table S2.6). In total, 285,010 (13.9%) children had a mother with a diabetes diagnosis before the index childbirth. The prevalence of maternal diabetes in this population increased from 6.6 % in 2004 to 11.8% in 2014. Mothers with diabetes were slightly older, more likely to have higher family income and to

live in urban areas. Children whose mothers had diabetes tended to have higher birthweight (Table S2.7).

For any cancer type, maternal type II diabetes or gestational diabetes did not elevate the risk in offspring. When we examined the effect on specific type of childhood cancer, we found an increased risk of glioma in offspring prenatally exposed to gestational diabetes compared to unexposed children (HR = 1.59, 95% CI: 1.01-2.50; Table 2.3). Relatively few mothers in Taiwan had a diagnosis of type II diabetes, and few glioma cases were identified in offspring in this subgroup of women.

We observed an increased risk of hepatoblastoma in offspring prenatally exposed to maternal type II diabetes compared to the unexposed (HR = 2.02, 95% CI: 1.02-4.00; Table 2.3).

An elevated point estimate of effect was also seen for ALL, CNS tumors, and retinoblastoma among offspring exposed to gestational diabetes with wide confidence intervals including the null value. Analysis with additional adjustment for maternal smoking resulted in largely similar results (Table S2.8).

Table 2.1 Maternal diabetes and childhood cancer risks in Denmark (birth year ≥ 1977)

	Total N	N (%)	Crude Model OR (95% CI)	Adjusted Model OR (95% CI)[a]
Controls	16,0484			
Type I diabetes		544 (0.3)	Ref.	Ref.
Type II diabetes		229 (0.1)	Ref.	Ref.
Gestational diabetes		1,014 (0.6)	Ref.	Ref.
Cases: All cancers	6,420			
Type I diabetes		29 (0.5)	1.34 (0.92, 1.94)	1.34 (0.92, 1.94)
Type II diabetes		15 (0.2)	1.62 (0.96, 2.73)	1.64 (0.97, 2.77)
Gestational diabetes		40 (0.6)	0.99 (0.72, 1.36)	0.98 (0.71, 1.35)
ALL	1,217			
Type I diabetes		6 (0.5)	1.45 (0.65, 3.25)	1.44 (0.64, 3.23)
Gestational diabetes		12 (1.0)	1.42 (0.80, 2.53)	1.38 (0.77, 2.45)
CNS	1,575			
Type I diabetes		13 (0.8)	2.44 (1.41, 4.24)	2.44 (1.40, 4.24)
Gestational diabetes		9 (0.6)	0.94 (0.48, 1.82)	0.95 (0.49, 1.84)
Gliomas	775			
Type I diabetes		6 (0.8)	2.34 (1.04, 5.24)	2.33 (1.04, 5.22)
Gestational diabetes		5 (0.7)	1.36 (0.56, 3.29)	1.38 (0.57, 3.36)

[a]Adjusted for birth year, sex, maternal age, birth order.

Note: Cancer types presented here have at least 5 cases exposed to maternal diabetes.

Table 2.2 The risk of central nervous system tumors among offspring of mothers with diabetes, stratified by age at diagnosis in Denmark

	Any diabetes		**Type I diabetes**	
Age groups of offspring (years)	N (%)	Adjusted Model OR (95% CI)[a]	N (%)	Adjusted Model OR (95% CI)[a]
0-14	16 (1.3)	1.06 (0.64, 1.74)	6 (0.5)	1.41 (0.63, 3.17)
15-19	9 (2.9)	3.63 (1.85, 7.13)	7 (2.2)	6.64 (3.08, 14.31)

[a]Adjusted for birth year and sex, maternal age, birth order

Table 2.3 Maternal diabetes and childhood cancer risks in Taiwan (2004-2014)

		Type II Diabetes			**Gestational Diabetes**		
	Total N	N (%)	Crude Model HR (95% CI)	Adjusted Model[a] HR (95% CI)	N (%)	Crude Model HR (95% CI)	Adjusted Model[a] HR (95% CI)
Non-cases	2,076,877	80,947 (3.9)	Ref.	Ref.	202,881 (9.8)	Ref.	Ref.
All cancers	2,160	64 (3.0)	0.82(0.64-1.05)	0.81(0.63-1.05)	211(9.8)	1.06(0.92-1.22)	1.06(0.92-1.22)
ALL	612	19(3.1)	0.88(0.56-1.38)	0.88(0.56-1.39)	64(10.5)	1.15(0.89-1.49)	1.16(0.89-1.51)
AML	155	4(2.6)	----------	----------	13(8.4)	0.90(0.51-1.59)	0.92(0.52-1.63)
NHL	438	14(3.2)	0.93(0.54-1.58)	0.82(0.48-1.40)	39(8.9)	0.98(0.70-1.36)	0.91(0.65-1.26)
CNS	293	8(2.7)	0.77(0.38-1.55)	0.78(0.39-1.59)	35(12.0)	1.33(0.94-1.90)	1.38(0.96-1.96)
Glioma	169	6(3.6)	1.03(0.45-2.32)	1.10(0.49-2.49)	22(13.0)	1.49(0.95-2.33)	1.59(1.01-2.50)
Retinoblastoma	129	< 3	----------	----------	18(14.0)	1.52(0.92-2.50)	1.48(0.90-2.44)
Medulloblastoma	69	< 3	----------	----------	6(8.7)	0.95(0.41-2.19)	0.96(0.41-2.22)
Neuroblastoma	226	9(4.0)	1.06(0.54-2.06)	1.00(0.51-1.96)	20(8.9)	0.92(0.58-1.44)	0.89(0.56-1.41)
Hepatoblastoma	113	9(8.0)	2.18(1.10-4.30)	2.02(1.02-4.00)	14(12.4)	1.32(0.75-2.30)	1.26(0.72-2.20)
Germ cell tumors	210	5(2.4)	0.66(0.27-1.61)	0.65(0.27-1.59)	14(6.7)	0.71(0.41-1.21)	0.70(0.41-1.21)

[a]Adjusted for birth year and sex, maternal age, parity.

2.5 Discussion

To our knowledge, the effect that maternal diabetes has on the risk of gliomas among offspring has not been reported previously. This is the first study to report on the risk of childhood cancer due to maternal diabetes in Taiwan. Relying on two population-based cancer registries covering several decades in Denmark and Taiwan, we assessed associations between maternal diabetes and childhood cancers. The distributions of types of diabetes were very different in the two populations, with type I diabetes being much more common in Denmark and type II and gestational diabetes more common in Taiwan, affecting our statistical power to estimate effects. Notably, in both Denmark and Taiwan, we observed increases in the risk of offspring developing gliomas, although this was related to different subtypes of diabetes. Thus, the increased risk for gliomas across different diabetes subtypes suggests that the mechanism of action may be related to fetal growth or the intrauterine environment rather than being solely related to autoimmune mechanisms in type I diabetes. Children prenatally exposed to other autoimmune diseases were not observed to have an increased risk of all childhood cancers combined, as reported previously.[40]

For gliomas, we observed a positive association with type I and gestational diabetes. Although increased risks were observed, the percentages of gliomas in offspring of women with any type of diabetes were low, with 0.6% and 0.09% among children in Denmark and Taiwan, respectively. Thus, our results between maternal type II diabetes and gliomas are limited by sample size. Results for maternal pregestational diabetes, gestational diabetes, and CNS tumors among offspring have previously been mixed.[43,113] Our results for CNS tumors were in line with a Finnish population-based registry study that reported a 1.37-fold increased CNS risk in

offspring of women with pregestational diabetes, and 1.19-fold increased CNS risk with gestational diabetes, both reported with some statistical uncertainty.[43] Unlike the present study, information was not available for the type of pregestational diabetes. Contrary to this, a population-based cohort study in Sweden [113] showed the risk of childhood brain tumors to be reduced with maternal type I diabetes and gestational diabetes for cases diagnosed before age 15. However, when cases diagnosed up to age 20 were included in their analysis, the negative association for maternal diabetes was attenuated and had wide confidence intervals. In our study, the associations between maternal diabetes (i.e., any types of diabetes, type I diabetes) and CNS tumors in offspring were stronger in children with age at diagnosis between 15 and 19 years than for those with age at diagnosis less than 15 years. This may be due to differences in the distribution of CNS tumors such as tumor behavior, primary site, and histology groups in the age groups.[138] Alternatively, genetic mechanism may provide explanations given that several loci related to diabetes traits was reported to be associated with cancers.

For retinoblastoma, our findings support the observation of a previous study that suggested a positive association between gestational diabetes and unilateral retinoblastoma in offspring with wide confidence intervals.[114] In contrast, no association of retinoblastoma with pregestational diabetes was reported in a study in California.[139] However, this study had limited statistical power, and underreporting of maternal diabetes on birth certificates in California is of concern.

In Taiwan, we observed an increase in the risk of hepatoblastoma among children prenatally exposed to type II diabetes. Similar to other regions in Asia, Taiwan exhibits a high rate of

hepatoblastoma in comparison to Europe [140] and the U.S.,[141] which enables us to investigate this cancer type in children in Taiwan. However, we had insufficient statistical power in the Danish analysis. Few studies reported on maternal diabetes and the risk of hepatoblastoma in children. In a study that observed elevated risks with type I or type II diabetes, the confidence interval was wide. [34] Prior associations with gestational diabetes were inconsistent.[34,142]

In our study, the increased risk for gliomas among children prenatally exposed to maternal diabetes in both populations suggest that factors that drive growth *in utero* may increase the risk of CNS tumors. In addition to the potential mechanism of action through birth weight, a recent meta-analysis found that gestational diabetes was consistently associated with higher maternal insulin-like growth factor-1 (IGF-I) concentrations.[143] In a prospective longitudinal study, IGF-1 concentrations were positively related to subsequent risk of gestational diabetes.[144] It has been shown that high maternal IGF-1 is consistently associated with fetal and placental growth and birthweight.[145-147] And IGF-1 has been strongly suggested to be involved in the pathogenesis of gliomas.[148]

The main strength of these studies is the reliance on population-based record data, avoiding the possibility of recall bias and minimizing selection bias. The relatively large sample sizes provided an opportunity to study subtypes of childhood cancer and allowed us to check and adjust for a number of covariates. This study was still limited by the small number of events resulting in imprecise effect estimates. Cancer types involving <10 exposed cases, as well as those with wide 95% confidence intervals, should be interpreted cautiously. In comparison to

another population-based study in Denmark,[44] maternal pregestational diabetes was underreported in our data. This is likely in part due to underdiagnosis of type I and II diabetes. This could lead to less precision in our effect estimates. In Taiwan, diabetes prevalence – were 0.1 % and 3.9 % for type I and type II diabetes before childbirth between 2004-2014, respectively; this is comparable to what has been reported in other population-based studies in Taiwan.[149,150] Based on previous validation studies, high positive predictive values were observed for ICD diagnoses of type I, type II and gestational diabetes in Denmark [151] and Taiwan.[152] However, we are aware that the more severe form of diabetes has a higher likelihood of being recorded in registers.[153] Furthermore, lower sensitivity when using information from the National Patient Register in Denmark alone to identify gestational diabetes may have caused non-differential exposure misclassification and resulted in an underestimation of the effect.[154] Finally, we did not have access to blood glucose measurements during pregnancy to determine whether glucose levels were adequately controlled. However, a previous study reported the validity of such measurements to be relatively low in Denmark.[155] In our data, birth weight was highest in children whose mothers had type II or gestational diabetes, suggesting that glucose levels were less than optimal in mothers with these types of diabetes. However, there is no evidence to suggest that glucose control during pregnancy modifies the risk of childhood cancer.

2.6 Conclusions

In conclusion, maternal diabetes increased the risk of certain childhood cancer in Denmark and Taiwan. Our study supports a potential role for maternal diabetes in cancer risk in offspring and implicates the importance of maintaining normal blood glucose levels to prevent rare but serious adverse health outcomes in the offspring.

2.7 Appendix

Table S2.1 ICD-8, ICD-9 and ICD-10 codes used to identify maternal diabetes

	ICD-8, ICD-9, ICD-10 Code	Definition
ICD-8	63474	Gestational diabetes mellitus
	Y6449	Gestational diabetes mellitus
	249	Type I diabetes
	250	Type II diabetes
ICD-9	250.x1, 250.x3	Type I diabetes
	250.0-250.9 except 250.x1-250.x3	Type II diabetes
	648.0, 648.8	Gestational diabetes mellitus
ICD-10	O24.4	Gestational diabetes mellitus
	O24.9	Unspecified diabetes mellitus in pregnancy, childbirth, and the puerperium
	O24.0	Pre-existing diabetes mellitus type 1
	O24.1	Pre-existing diabetes mellitus type 2
	O24.3	Pre-existing diabetes mellitus, unspecified
	O24.8	Other pre-existing diabetes mellitus
	H36.0	Diabetic retinopathy
	E10	Insulin-dependent diabetes mellitus
	E11	Type 2 diabetes mellitus
	E12	Malnutrition-related diabetes mellitus
	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus

Table S2.2 Demographic characteristics of study participants in Denmark, by case control status, 1977-2013 (n=166,904)

	Cases (N = 6,420)	**Controls** (N = 160,484)
	N (%)	N (%)
Mother's diabetes type		
Type 1 diabetes	29 (0.5)	544 (0.3)
Type 2 diabetes	15 (0.2)	229 (0.1)
GDM	40 (0.6)	1014 (0.6)
Mother pre-pregnancy BMI		
Mean (SD)	24.4 (5.5)	24.1 (4.8)
≤ 18.4	34 (4.2)	821 (4.1)
18.5-25	497 (61.1)	12924 (64.4)
25-30	179 (22.0)	4043 (20.1)
30 +	103 (12.7)	2279 (11.4)
Maternal age		
Mean (SD)	28.4 (5.0)	28.3 (5.0)
≤ 24	1423 (22.2)	36923 (23.0)
25-29	2472 (38.5)	60759 (37.9)
30-34	1744 (27.2)	44546 (27.8)
35-39	669 (10.4)	15695 (9.8)
40+	112 (1.7)	2561 (1.6)
Paternal age		
Mean (SD)	31.2 (5.8)	31.1 (5.8)
≤ 24	661 (10.4)	17979 (11.3)
25-29	2047 (32.1)	50022 (31.3)
30-34	2050 (32.1)	52045 (32.6)
35-39	1096 (17.2)	26766 (16.8)
40+	526 (8.2)	12842 (8.0)
Family SES		
Academics and high level self-employed	621 (13.3)	15176 (13.0)
Middle-long education	807 (17.3)	19178 (16.4)
Shorter education	879 (18.8)	22312 (19.0)
Skilled worker	1512 (32.4)	38330 (32.7)
Unskilled worker	846 (18.1)	22187 (18.9)
Birth order		
1	2827 (44.0)	68852 (42.9)
2	2400 (37.4)	60938 (38.0)
3 or more	1193 (18.6)	30694 (19.1)

Maternal smoking at the first prenatal visit	818 (23.9)	20753 (24.2)
Child's birthweight (g)		
Mean (SD)	3466.5 (607.9)	3437.8 (585.8)
Extremely low (<1000g)	48 (0.8)	944 (0.6)
Low (1000-2500g)	274 (4.3)	6947 (4.3)
Medium (2500g-4000g)	4846 (75.9)	125336 (78.4)
High (>4000g)	1219 (19.1)	26606 (16.6)
Maternal birthplace		
Denmark	5853 (91.3)	146777 (91.6)
Other Europe	217 (3.4)	5523 (3.4)
Other	338 (5.3)	7893 (4.9)
Urban or rural birthplace		
Urban	2114 (32.9)	50981 (31.8)
Small towns	1808 (28.2)	46632 (29.1)
Rural	2498 (38.9)	62871 (39.2)

Table S2.3 Demographic characteristics of study participants, stratified by maternal diabetes status, in Denmark, 1977-2013 (N = 166,904)

	Children whose mother had diabetes (N = 1,948)	**Children whose mother without diabetes (N = 164,956)**
	N (%)	N (%)
Mother pre-pregnancy BMI	28.6 (6.3)	24.0 (4.7)
18.4 or less	10 (1.6)	845 (4.2)
18.5-25	191 (29.8)	13230 (65.4)
25-30	202 (31.5)	4020 (19.9)
30 +	239 (37.2)	2143 (10.6)
Child's sex		
Male	1047 (53.7)	90340 (54.8)
Female	901 (46.3)	74616 (45.2)
Maternal age		
Mean (SD)	30.9 (5.2)	28.3 (4.9)
≤ 24	219 (11.2)	38127 (23.1)
25-29	618 (31.7)	62613 (38.0)
30-34	598 (30.7)	45692 (27.7)
35-39	397 (20.4)	15967 (9.7)
40+	116 (6.0)	2557 (1.6)
Paternal age		
Mean (SD)	33.5 (6.4)	31.0 (5.8)
≤ 24	97 (5)	18543 (11.3)
25-29	458 (23.6)	51611 (31.5)
30-34	597 (30.8)	53498 (32.6)
35-39	477 (24.6)	27385 (16.7)
40+	311 (16)	13057 (8)
Family SES		
Academics and high level self-employed	108 (9.1)	15689 (13.0)
Middle-long education	172 (14.5)	19813 (16.4)
Shorter education	232 (19.6)	22959 (19.0)
Skilled worker	403 (34.0)	39439 (32.7)
Unskilled worker	270 (22.8)	22763 (18.9)
Birth order		
1	669 (34.3)	71010 (43.0)
2	800 (41.1)	62538 (37.9)
3 or more	479 (24.6)	31408 (19.0)
Maternal smoking at the first prenatal visit	303 (21.3)	21268 (24.2)

Child's birthweight (g)		
Mean (SD)	3512.6 (684.7)	3438.0 (585.4)
Extremely low (<1000g)	13 (0.7)	979 (0.6)
Low (1000-2500g)	122 (6.3)	7099 (4.3)
Medium (2500g-4000g)	1339 (68.9)	128843 (78.4)
High (>4000g)	468 (24.1)	27357 (16.7)
Maternal birthplace		
Denmark	1661 (85.4)	150969 (91.7)
Other Europe	62 (3.2)	5678 (3.4)
Other	222 (11.4)	8009 (4.9)
Urban or rural birthplace		
Urban	688 (35.3)	52407 (31.8)
Small towns	489 (25.1)	47951 (29.1)
Rural	771 (39.6)	64598 (39.2)

Table S2.4 Sensitivity analysis examining the associations of type I diabetes and gestational diabetes with childhood cancer risks in Denmark (1991+, N = 89,232)

	Type I Diabetes			
	Total N	N (%) with type I diabetes	Adjusted Odds Ratio (95% Confidence Interval)[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
Controls	85813	289 (0.3)	Ref.	Ref.
All cancers	3419	14 (0.4)	1.21 (0.71, 2.08)	1.21 (0.71, 2.08)
ALL	682	5 (0.7)	2.14 (0.88, 5.19)	2.14 (0.88, 5.20)
CNS	812	7 (0.9)	2.60 (1.22, 5.52)	2.60 (1.22, 5.52)
Gliomas	341	5 (1.5)	4.51 (1.85, 11.0)	4.51 (1.85, 11.0)
	Gestational Diabetes			
	Total N	N (%) with gestational diabetes	Adjusted Odds Ratio (95% Confidence Interval)[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
Controls	85813	908 (1.1)	Ref.	Ref.
All cancers	3419	38 (1.1)	1.05 (0.76, 1.46)	1.05 (0.76, 1.46)
ALL	682	12 (1.8)	1.49 (0.83, 2.65)	1.49 (0.83, 2.65)
CNS	812	8 (1.0)	0.96 (0.47, 1.93)	0.95 (0.47, 1.93)
Gliomas	341	< 5	-----	-----

[a]Adjusted for birth year and sex, maternal age, birth order

[b]Additionally adjusted for maternal smoking

Table S2.5 Sensitivity analysis examining the associations of pregestational diabetes and gestational diabetes with childhood cancer risks in Denmark (2003+, N = 20,880)

	Pregestational Diabetes			
	Total N	N (%) with pregestational diabetes	Adjusted Odds Ratio (95% Confidence Interval)[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
Controls	20067	149 (0.7)	Ref.	Ref.
All cancers	813	7 (0.9)	1.17 (0.54, 2.50)	1.13 (0.53, 2.42)
ALL	201	< 5	----	----
CNS	186	< 5	----	----
Gliomas	64	< 5	----	----
	Gestational Diabetes			
	Total N	N (%) with gestational diabetes	Adjusted Odds Ratio (95% Confidence Interval)[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
Controls	20067	465 (2.3)	Ref.	Ref.
All cancers	813	21 (2.6)	1.12 (0.72, 1.75)	1.05 (0.67, 1.64)
ALL	201	8 (4.0)	1.70 (0.83, 3.49)	1.74 (0.84, 3.61)
CNS	186	< 5	----	----
Gliomas	64	< 5	----	----

[a]Adjusted for birth year and sex, maternal age, birth order

[b]Additionally adjusted for pre-pregnancy BMI

Note: Due to limited sample size, we were not able to examine the change in the estimates with and without adjustment of pre-pregnancy BMI for the association between maternal type I diabetes and any subtype or all types of childhood cancer, so the results presented here combined all types of pregestational diabetes.

Table S2.6 Demographic characteristics of cancer cases and controls in Taiwan, birth years 2004-2014

	Cancer Cases N=2,160 N (%)	**Non-cases N=2,076,877** N (%)
Maternal diabetes		
Type I diabetes	< 3	2372(0.1)
Type II diabetes	64 (3.0)	80947(3.9)
Gestational diabetes	211 (9.8)	202881(9.8)
Birth year		
2004	291 (13.5)	199381 (9.6)
2005	297 (13.8)	191774 (9.2)
2006	249 (11.5)	190892 (9.2)
2007	252 (11.7)	192909 (9.3)
2008	222 (10.1)	187788 (9.0)
2009	230 (10.6)	185401 (8.9)
2010	141 (6.5)	151020 (7.3)
2011	155 (7.2)	182461 (8.8)
2012	156 (7.2)	205961 (9.9)
2013	92 (4.3)	191559 (9.2)
2014	75 (3.5)	197731 (9.5)
Maternal age		
Mean (SD)	30.0 (4.8)	30.2 (4.8)
<20	41 (1.9)	31044 (1.5)
20-29	956 (44.3)	863624 (41.6)
30-34	804 (37.2)	797993 (38.4)
35-39	291 (13.5)	331300 (16.0)
40+	68 (3.2)	52916 (2.6)
Maternal history of cancer		
Yes	43 (2.0)	31809 (1.5)
Paternal age		
Mean (SD)	33.1 (5.5)	33.2 (5.3)
<20	5 (0.2)	3485 (0.2)
20-29	510 (23.6)	454359 (21.9)
30-34	779 (36.1)	760634 (36.6)
35-39	479 (22.2)	511717 (24.6)
40+	242 (11.2)	220401 (10.6)
Missing	145 (6.7)	126281 (6.1)

Paternal history of cancer		
Yes	34 (1.6)	22987(1.1)
Family income (New Taiwan dollar)		
<26400	554 (25.7)	498013 (24.0)
26400-45600	542 (25.1)	497747 (24.0)
45600-70850	488 (22.6)	500029 (24.1)
≥70850	485 (22.5)	498801(24.0)
Missing	91 (4.2)	82287 (4.0)
Urbanization level of inhabited area		
High	1078 (50.0)	1102672 (53.1)
Middle	876 (40.6)	781604 (37.6)
Low	206 (9.5)	192601 (9.3)
Mother's birthplace		
Taiwan	1302 (60.3)	1400491 (67.4)
Foreign born	141 (6.5)	132170 (6.4)
Missing	717 (33.2)	544216 (26.2)
Sex		
Male	1197 (55.4)	1079059 (52.0)
Female	963 (44.6)	997718 (48.0)
Missing	0 (0.0)	100 (7.5)
Birth weight (g)		
Mean (SD)	3070.6 (485.6)	3078.1 (449.5)
<2500	185 (8.6)	156525 (7.5)
2500-3999	1926 (89.2)	1882670 (90.7)
≥4000	49 (2.3)	37682 (1.8)
Gestational age (weeks)		
Mean (SD)	38.1 (1.9)	38.3 (1.7)
Very preterm (<33)	45 (2.1)	23053 (1.1)
Preterm (33-36)	199 (9.2)	160438 (7.7)
Term (≥37)	1916 (88.7)	1893386 (91.2)
Size for gestational age		
Lowest 10%	185 (8.6)	195988 (9.4)
Middle 80%	1785 (82.6)	1712398 (82.5)
Highest 10%	190 (8.8)	168491 (8.1)
Method of delivery		
Vaginal	1355 (62.7)	1331991 (64.1)
Cesarean section	805 (37.3)	744886 (35.9)

Multiple birth		
Singleton	2087 (96.6)	2015039 (97.0)
Twin or more	73 (3.4)	61838 (3.0)
Parity		
1	832 (38.5)	807516 (38.9)
2	1010 (46.8)	1044027 (50.3)
3 or more	318 (14.7)	225334 (10.9)

Table S2.7 Demographic characteristics and maternal diabetes in Taiwan (n= 2,079,037)

	Cases (n=2,160)			Non-cases (n=2,076,877)		
	Children of mothers with maternal diabetes (n=276)	Children of mothers without maternal diabetes (n=1,867)	Missing (n=17)	Children of mothers with maternal diabetes (n=284,734)	Children of mothers without maternal diabetes (n=1,769,535)	Missing (n=22,608)
	N (%)	N (%)		N (%)	N (%)	
Birth year						
2004	24(8.7)	264(14.1)	≤ 3	18885(6.6)	177494(10.0)	3002
2005	35(12.7)	258(13.8)	4	20156(7.1)	169233(9.6)	2385
2006	32(11.6)	214(11.5)	≤ 3	21818(7.7)	166947(9.4)	2127
2007	30(10.9)	219(11.7)	≤ 3	24163(8.5)	166520(9.4)	2226
2008	30(10.9)	188(10.1)	≤ 3	24395(8.6)	161327(9.1)	2066
2009	26(9.42)	204(10.9)	≤ 3	26365(9.3)	157109(8.9)	1927
2010	16(5.8)	125(6.7)	≤ 3	22684(8.0)	126698(7.2)	1638
2011	27(9.8)	128(6.9)	≤ 3	28542(10.0)	152215(8.6)	1704
2012	22(8.0)	134(7.2)	≤ 3	32692(11.5)	171488(9.7)	1781
2013	20(7.3)	72(3.9)	≤ 3	31469(11.1)	158250(8.9)	1840
2014	14(5.1)	61(3.3)	≤ 3	33565(11.8)	162254(9.2)	1912
Child's sex						
Male	146(52.9)	1047(56.1)	4	149565(52.5)	917656(51.9)	11838
Female	130(47.1)	820(43.9)	13	135156(47.5)	851792(48.1)	10770
missing	≤ 3	≤ 3	≤ 3	13	87	≤ 3
Maternal age						
Mean (SD)	31.3(4.6)	29.8(4.9)	17	31.5(4.6)	30.0(4.8)	22608
<20	≤ 3	38(2.0)	≤ 3	1728(0.6)	29202(1.7)	114
20-29	94(34.1)	854(45.7)	8	89330(31.4)	761712(43.1)	12582
30-34	112(40.6)	683(36.6)	9	120620(42.4)	670635(37.9)	6738
35-39	55(19.9)	236(12.6)	≤ 3	61402(21.6)	267143(15.1)	2755

40+	12(4.4)	56(3.0)	≤ 3	11654(4.1)	40843(2.3)	419
Paternal age						
Mean (SD)	34.1(5.0)	32.9(5.5)	17	34.1(5.2)	33.1(5.3)	22608
<20	≤ 3	5(0.3)	≤ 3	182(0.1)	3298(0.2)	5
20-29	44(16.8)	462(26.6)	4	47880(17.6)	403843(24.4)	2636
30-34	93(35.5)	679(39.1)	9	105548(38.8)	648175(39.1)	6911
35-39	85(32.4)	392(22.6)	0	81619(30.0)	423297(25.6)	6801
40+	40(15.3)	198(11.4)	4	36717(13.5)	177940(10.7)	5744
Missing	14	131	≤ 3	12788	112982	511
Family income (New Taiwan dollar)						
<26400	55(20.5)	488(27.4)	11	53648(19.4)	428844(25.3)	15521
26400-45600	67(25.0)	471(26.4)	6	65789(23.8)	428133(25.3)	3825
45600-70850	63(23.5)	423(23.7)	0	73012(26.4)	424827(25.1)	2190
≥70850	83(31.0)	402(22.5)	≤ 3	84075(30.4)	413936(24.4)	790
Missing	8	83	≤ 3	8210	73795	282
Urbanization level of inhabited area						
High	150(54.4)	918(49.2)	10	164073(57.6)	926023(52.3)	12576
Middle	97(35.1)	772(41.4)	7	93242(32.8)	680369(38.5)	7993
Low	29(10.5)	177(9.5)	≤ 3	27419(9.6)	163143(9.2)	2039
Parity						
1	107(38.8)	716(38.4)	9	112315(39.5)	681598(38.5)	13603
2	130(47.1)	872(4.67)	8	145842(51.2)	890263(50.3)	7922
3 or more	39(14.1)	279(14.9)	≤ 3	26577(9.3)	197674(11.2)	1083
Maternal smoking (before birth)						
Yes	≤ 3	8(0.4)	≤ 3	2319(0.8)	11478(0.7)	≤ 3
No	276(100.0)	1859(99.6)	≤ 3	282415(99.2)	1758057(99.4)	437
Missing	≤ 3	≤ 3	17	≤ 3	≤ 3	22171
Child's birthweight						

Mean (SD)	3128.7(468.6)	3061.4(488.7)	17	3116.3(466.6)	3070.8(446.5)	22608
Extremely low (<1000g)	17(6.2)	11(0.6)	≤ 3	350(0.1)	4188(0.2)	36
Low (1000-2500g)		175(9.4)	≤ 3	22042(7.7)	143564(8.1)	1218
Medium (2501g-4000g)	249(90.2)	1650(88.4)	17	254864(89.5)	1596961(90.3)	20869
High (>4000g)	10(3.6)	31(1.7)	≤ 3	7478(2.6)	24822(1.4)	485
Mother's diabetes type						
Type 1 diabetes	65(23.5)	--------	≤ 3	2372(0.8)	--------	≤ 3
Type 2 diabetes		--------	≤ 3	80947(28.1)	--------	≤ 3
GDM	211(76.5)	--------	≤ 3	202881(71.1)	--------	≤ 3

Table S2.8 Sensitivity analysis examining the associations of type II diabetes and gestational diabetes with childhood cancer risks in Taiwan (2004-2014)

		Type II Diabetes			Gestational Diabetes		
	Total N	N (%)	Crude HR (95% CI)	Adjusted Model HR (95% CI)[a]	N (%)	Crude HR (95% CI)	Adjusted Model HR (95% CI)[a]
Non-cases	2076877	80947 (3.9)	Ref.	Ref.	202881 (9.8)	Ref.	Ref.
All cancers	2160	64(3.0)	0.82(0.64-1.05)	0.82(0.64-1.05)	211(9.8)	1.06(0.92-1.22)	1.06(0.92-1.22)
ALL	612	19(3.1)	0.88(0.56-1.38)	0.88(0.56-1.40)	64(10.5)	1.15(0.89-1.49)	1.16(0.89-1.51)
AML	155	4(2.6)	----------	----------	13(8.4)	0.90(0.51-1.59)	0.92(0.52-1.63)
NHL	438	14(3.2)	0.93(0.54-1.58)	0.82(0.48-1.40)	39(8.9)	0.98(0.70-1.36)	0.91(0.65-1.26)
Central nervous system tumors	293	8(2.7)	0.77(0.38-1.55)	0.79(0.39-1.59)	35(12.0)	1.33(0.94-1.90)	1.38(0.96-1.96)
Gliomas	169	6(3.6)	1.03(0.45-2.32)	1.10(0.49-2.49)	22(13.0)	1.49(0.95-2.33)	1.59(1.01-2.50)
Retinoblastoma	129	≤ 3	----------	----------	18(14.0)	1.52(0.92-2.50)	1.48(0.90-2.44)
Medulloblastoma	69	≤ 3	----------	----------	6(8.7)	0.95(0.41-2.19)	0.96(0.41-2.22)
Neuroblastoma	226	9(4.0)	1.06(0.54-2.06)	1.00(0.51-1.96)	20(8.9)	0.92(0.58-1.44)	0.89(0.56-1.41)
Hepatoblastoma	113	9(8.0)	2.18(1.10-4.30)	2.02(1.02-4.00)	14(12.4)	1.32(0.75-2.30)	1.26(0.72-2.20)
Germ cell tumors	210	5(2.4)	0.66(0.27-1.61)	0.66(0.27-1.59)	14(6.7)	0.71(0.41-1.21)	0.70(0.41-1.21)

[a]Adjusted for birth year and sex, maternal age, parity, maternal smoking.

Chapter 3. Maternal occupational physical activity during pregnancy and childhood cancers in Denmark 1968–2013

3.1 Abstract

Objective To examine associations with maternal occupational physical activity exposure during pregnancy and childhood cancer risk in offspring.

Methods: We included all cancer cases born in Denmark between 1968 and 2013, aged 0–19 at diagnosis, and diagnosed between 1968 and 2016 (N= 7,077). Controls, randomly selected from the Central Population Registry, were individually matched by birth year and sex (ratio 1:25). Maternal occupational physical activity was assessed by a job exposure matrix based on the Nordic Occupational Cancer Study (score: heavy or rather heavy physical work versus all other levels). Unconditional logistic regression adjusted for potential confounders was used to estimate potential effects.

Results: Heavy maternal occupational physical activity during pregnancy was associated with a higher risk of medulloblastoma (adjusted odds ratio=1.85, 95% confidence interval: 1.28-2.66) and the increase was consistent across occupational groups. A dose-response pattern was observed for medulloblastoma, with an increase in the risk in the highest intensity group (adjusted odds ratio = 2.47; 95% confidence interval: 1.35–4.52), in the medium intensity group (adjusted odds ratio = 1.61; 95% confidence interval: 1.03–2.53), and a moderate increase in the low intensity group with a wide confidence interval (adjusted OR = 1.99; 95% confidence interval: 0.92–4.30). Among healthcare professionals only, heavy maternal occupational physical activity increased the risk of melanoma in offspring (adjusted odds ratio =1.52, 95% confidence interval: 1.00-2.30), but there was no dose-response gradient observed.

Conclusion: Heavy maternal occupational physical activity in Denmark appear to be associated with an increased risk of medulloblastoma and possibly melanoma in the offspring. If associations are corroborated, regulations that aim to protect pregnant women from being exposed to high levels of physical activity at work should be considered.

3.2 Introduction

Occupational physical activity (OPA) and leisure time physical activity (LTPA) have contrasting health effects. As concluded by International Agency for Research on Cancer, physical activity has protective effects against colon and breast cancer.[156] LTPA reduces the risk of lung [157], pancreatic [158] and endometrial cancer [159] as well as colon and breast cancer.[160] The protective effects of LTPA may extend to other 9 cancer types (not including pancreatic cancer) as reported in a large study using data from 12 cohorts in the US and Europe.[161] Although beneficial effects of LTPA have been observed among adults, OPA may have a harmful effect on health outcomes including all-cause mortality, myocardial infarction, and possibly several cancer types including cervical and lung cancer.[162-165] While LTPA decreases blood pressure to variable degrees,[166] OPA that may be including heavy lifting or static postures instead elevates blood pressure. In addition, OPA may occur without sufficient cardiovascular recovery time due to a lack of control over job tasks. Thus, disparities of the health effects of LTPA versus OPA may be explained by the differences in intensity, duration and type of physical activity that may affect human physiology very differently.

The prevalence of OPA exposures among pregnant women is high. In the US, prolonged standing (> 30 hours per week) was reported by 25.2% and 19.9% of women during their first and second trimesters, respectively, and the percentage of women with repetitive lifting (≥ 13 times per week) was 9.7% in the first trimester and 5.8% in the second trimester.[167] In Denmark, more than 25% of all pregnant women lifted loads >10 kg at work daily and 12% loads >20 kg.[53] A high level of maternal OPA including physically demanding work, prolonged standing and walking, lifting and carrying, as well as shift and night work and high cumulative work fatigue

were associated with adverse birth outcomes, including preterm birth and low birthweight.[49-51,54,55,168,169]

Even though childhood cancer is a rare disease, the incidence rates of childhood cancer have been rising across the past few decades worldwide.[1] Prenatal exposure to radiation [4] and diethylstilbestrol [5] increase the risk of childhood cancers, but account for a small number of cases. Other suspected risk factors include maternal age, maternal comorbidities (e.g., infections) and medication use but associations are less established and vary across cancer types.[170-172] Restricted fetal growth and preterm birth are known risk factors for several childhood cancers.[137] To the best of our knowledge, no published studies have examined whether maternal LTPA or OPA during pregnancy affect childhood cancer risks. Yet, prior studies which focused on job titles have indicated that maternal occupations that require a lot of standing, walking or dynamic movement are related to a higher risk for childhood cancer in offspring (e.g., agricultural workers, assistant nurses, cooks, factory workers, pharmacists, pig farmers, sales, teachers and daycare workers, textile industry workers).[59,60,62,63,65,67-69] Although chemical or non-chemical agents encountered in these occupational settings may in part explain these results, the role of OPA has not been considered.

Understanding the long-term consequences of maternal physical activity at work on children's health is crucial to shape work policy that protects pregnant women and their children. Therefore, we investigated associations between maternal OPA and childhood cancer risk among offspring using registers in Denmark. We hypothesized that maternal occupational physical activity may increase the risk of certain types of childhood cancer, especially cancer types that

have previously been related to fetal growth such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) medulloblastoma, astrocytoma, Wilms tumor and neuroblastoma.[173-176]

3.3 Methods

Data sources and study population

We included all cancer cases born between 1968 and 2013, aged 0–19 at diagnosis, and diagnosed between 1968 and 2016. Controls, randomly selected from the Central Population Registry, were frequency-matched by birth date and sex (ratio 1:25) and were free of cancer at the date of diagnosis of their corresponding case. Pregnancies that were likely not viable (gestational age ≤ 20 weeks or birth weight < 500g, n = 18) were excluded. The cases and controls were linked to the Supplementary Pension Fund Register, the Medical Births Register and the Danish National Patient Register based on their unique Central Person number assigned at birth to retrieve maternal employment history and covariates information. The Danish Prescription Register, available for a part of the study period (1995+) only, was used to identify medication use during pregnancy.

Cancer diagnosis was based on a Danish modification of the International Classification of Diseases, Revision 7 before 1978, a converted version of ICD-7 to ICD-10 until 2004, and subsequently ICD-10, while morphology and topography were recorded according to International Classification of Childhood Cancer, ICCC-1 and ICCC-3.[177]

Exposure assessments

Maternal employment during pregnancy was obtained from the Supplementary Pension Fund Register. The Supplementary Pension Fund Register was founded in 1964 and keeps records of mandatory pension contributions for all employees in Denmark. [178] The employment history is recorded of residents between 18–66 years old that work ≥ 9 h/week; from 1978 also aged 16–17 years was included in the register. Self-employed persons are not required to participate in the Supplementary Pension fund. This register keeps records of the name, start and end dates of each job, and a unique 8-digit company number. Companies have been classified into industry code (Danmarks Statistiks Erhvervsgrupperingskode, DSE-77), corresponding to an extended version of the International Standard Industrial Classification of all Economic Activities from 1968.[179]

We applied job-exposure matrices that were developed for Denmark as a part of the Nordic Occupational Cancer Study (NOCCA-DANJEM),[180] an adaptation of a Finnish job exposure matrix. This job exposure matrix was adapted to the Danish working population based on thousands of measurements and observations of occupational exposures. OPA exposures of industries were assessed by self-reported heavy or rather heavy physical work in a national interview survey. If more than 10% respondents in the industry reported heavy or rather heavy physical work, the industry was set as being exposed to OPA. We will use "heavy OPA" forthwith to describe this category.

During pregnancy, women who were not employed in industries identified by the NOCCA-DANJEM as being exposed to any heavy OPA were used as the reference group. Women who were ever employed in industries identified by the NOCCA-DANJEM as being exposed to any

heavy OPA were in the exposed group. To quantify exposure intensity, we retrieved the average proportion (P) and level (L) of heavy OPA of each industry code from the NOCCA-DANJEM and calculated the product (P * L) to generate exposure intensity, which we log transformed to achieve a normal distribution. The level of heavy OPA was measured as a score which was close to 1 if most respondents in the industry reported very heavy work and was close to 0 if most respondents in the industry reported only fairly heavy work. We present results among unexposed and ever exposed individuals, with ever exposure further categorized into low, moderate, and high intensity. Values of heavy OPA intensity in the 0-25th percentile were categorized as "low," the 25-75th percentile as "moderate," and >75th percentile as "high".

Cases and controls were excluded from our study population if mothers did not work during their pregnancy (n=26,110), resulting in 7,077 cases and 183,611 controls for the final analyses. We conducted a sensitivity analysis in which we included these cases and controls and considered their mothers as unexposed.

Statistical Analysis

Unconditional logistic regression analyses were used to estimate associations with heavy maternal OPA during pregnancy and childhood cancer in offspring. We utilized unconditional logistic regression, breaking the matching, to improve statistical power.[135] We adjusted for maternal age in the final model because of its role as a potential risk factor for many types of childhood cancer and its associations with heavy maternal OPA exposures observed in the present study.[170] We also considered adjustment for other covariates, including family

socioeconomic status, maternal birth place (Denmark/Europe/Other), maternal viral infections, mother's cancer diagnosis before birth, maternal smoking status (1991+), and maternal BMI (2003+) but no evidence of confounding was observed using the criterion of 10% for the change in estimate.

The most common industry with heavy OPA among study participants' mothers was healthcare (55.1%). Therefore, we also examined the effect of heavy maternal OPA separately in the subgroups of healthcare professionals and non-healthcare professionals.

We conducted several sensitivity analyses. In our data, heavy maternal OPA was highly correlated with welding fumes, iron, methylene chloride, sulfur dioxide, chromium, night shift work, gasoline and nickel (tetrachoric correlation =0.99; 0.99; 0.99; 0.98; 0.99; 0.96; 0.82; 0.84, respectively). Among these exposures, welding fumes, iron, sulfur dioxide, chromium, and nickel have been related to childhood cancer risk.[181,182] Therefore in a sensitivity analysis, mothers were excluded if they were exposed to any of these occupational exposures during pregnancy. Further, OPA exposures could potentially increase the use of certain medications such as pain relievers.[183] To address the impact of medication use associated with OPA exposures during pregnancy which might be related to childhood cancer risk, we examined the pattern of medication use by exposure groups and case control status. All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

Regarding demographic characteristics, cases and controls were largely similar (Table 3.1). Mothers of cases smoked less than controls and were more likely to be overweight (Table 3.1). The mothers in our study exposed to heavy OPA during pregnancy were most often employed in hospitals, with smaller numbers employed in telegraph and telephone services, in the fish production industry, in manufacturing or in the police or judicial system (Table S3.1).

For medulloblastoma, an increased risk was observed in offspring whose mother performed any heavy OPA during pregnancy (adjusted odds ratio [OR] = 1.85; 95% confidence interval [CI]: 1.28–2.66; Table 3.2). An increase in the risk of AML was also observed but the confidence intervals were wide (Table 3.2). In stratified analyses, similar increases in the risk of medulloblastoma were observed among healthcare professionals and non-healthcare professionals exposed to any heavy OPA (Table 3.2). An increase in the risk of melanoma with any heavy OPA was observed among healthcare professionals only (adjusted OR=1.52, 95% CI: 1.00-2.30; Table 3.2). After adjustment for maternal history of melanoma (1963-2016), this increase remained (adjusted OR=1.51, 95% CI: 1.00- 2.29). In addition, an increased risk of ALL with wide confidence intervals was observed among non-healthcare professionals only while an increased risk of retinoblastoma with wide confidence intervals was observed among healthcare professionals only for any heavy OPA (Table 3.2).

The intensity of heavy OPA was positively associated with medulloblastoma with an indication of dose-response, with the highest risk observed in the high intensity exposure group (adjusted OR = 2.47, 95% CI: 1.35-4.52; Table 3.3), a moderate risk in the medium intensity exposure

group (adjusted OR = 1.61, 95% CI: 1.03-2.53; Table 3.3); a moderate risk increase was also seen with low intensity exposure but the confidence interval was wide (adjusted OR = 1.99, 95% CI: 0.92-4.30; Table 3.3). An increase in the risk of ALL was observed only in the group with high intensity exposure (adjusted OR = 1.38, 95% CI: 1.02-1.87; Table 3.3). The risk of melanoma was moderately increased in the group with medium intensity, with no evidence of association in the high intensity group (Table 3.3).

When we considered mothers who did not work during pregnancy as unexposed to heavy OPA and included them in analyses, results did not change (data not shown). After excluding occupations with chemical exposures correlated with heavy OPA during pregnancy, we did not see a substantial change in the point estimate for medulloblastoma risk (Table S3.2). Subgroup analyses of other cancer types in non-healthcare and healthcare professionals were reported in Table S3.3. The associations between the intensity of heavy OPA and the risk of other childhood cancer subtypes can be found in Table S3.4. We examined prescription medication use during pregnancy by maternal OPA exposure groups and compared medulloblastoma case and control mothers, however the distributions of the most frequently used medications (salbutamol, hydrocortisone, salmeterol and fluticasone) were similar across exposure and case/control groups. In addition, no single medication class was taken by more than 5 medulloblastoma case mothers.

Table 3.1 Characteristics of population in the perinatal period, 1968-2013

Demographic characteristics	Cases (N= 7,077)		Controls (N= 183,611)	
	N (%)	Mean (SD)	N (%)	Mean (SD)
Infant's sex				
Female	3147 (44.5)		81591 (44.4)	
Male	3930 (55.5)		102020 (55.6)	
Maternal age at birth of index child (years)		28.4 (5.0)		28.3 (5.0)
24 or less	1961 (27.7)		51843 (28.2)	
25-29	2719 (38.4)		69655 (37.9)	
30-34	1688 (23.9)		44947 (24.5)	
35-39	612 (8.6)		14919 (8.1)	
40+	97 (1.4)		2247 (1.2)	
Paternal age at birth of index child (years)		31.2 (5.8)		31.1 (5.8)
24 or less	977 (13.9)		26468 (14.5)	
25-29	2453 (34.9)		62054 (34.0)	
30-34	2078 (29.5)		55314 (30.3)	
35-39	1026 (14.6)		26578 (14.5)	
40+	499 (7.1)		12318 (6.7)	
Family socioeconomic status				
Academics and high level self-employed	752 (13.2)		18782 (12.8)	
Middle-long education	1008 (17.6)		24773 (16.9)	
Shorter education	1101 (19.2)		28293 (19.3)	
Skilled worker	1867 (32.7)		47872 (32.7)	
Unskilled worker	991 (17.3)		26672 (18.2)	
Maternal birthplace				
Denmark	6582 (93.2)		171042 (93.3)	
Europe	217 (3.1)		6001 (3.3)	
Other	260 (3.7)		6188 (3.4)	
Child's birthplace				
Urban	2477 (35.0)		60522 (33.0)	
Small town	2229 (31.5)		59311 (32.3)	
Rural	2371 (33.5)		63778 (34.7)	
First born	586 (8.3)		14459 (7.9)	
Maternal history of cancer	166 (2.3)		3743 (2.0)	
Maternal viral infections	193 (2.7)		4418 (2.4)	
Maternal smoking at the first prenatal visit (1991+)	600 (22.6)		17689 (23.7)	
Maternal overweight (2003+)	223 (34.0)		5260 (31.3)	

Table 3.2 Odds ratios (95% confidence intervals) for childhood cancer risk and maternal OPA during pregnancy, stratifying by healthcare and non-healthcare professionals, 1968-2013

Cancer type	Total	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
All study population				
Controls	183611	32226 (17.6)	Ref.	Ref.
All cancers	7077	1258 (17.8)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
ALL	1305	244 (18.7)	1.12 (0.95, 1.32)	1.11 (0.95, 1.31)
AML	280	60 (21.4)	1.33 (0.94, 1.87)	1.32 (0.94, 1.86)
Hodgkin	403	70 (17.4)	0.90 (0.67, 1.21)	0.89 (0.66, 1.21)
NHL	128	22 (17.2)	0.69 (0.36, 1.29)	0.69 (0.37, 1.30)
CNS	1718	296 (17.2)	1.01 (0.88, 1.17)	1.01 (0.88, 1.17)
Gliomas	906	164 (18.1)	1.07 (0.89, 1.30)	1.08 (0.89, 1.30)
Medulloblastoma	198	52 (26.3)	1.84 (1.28, 2.64)	1.85 (1.28, 2.66)
Neuroblastoma	285	47 (16.5)	0.84 (0.58, 1.21)	0.84 (0.58, 1.20)
Retinoblastoma	139	28 (20.1)	1.32 (0.81, 2.15)	1.32 (0.81, 2.16)
Rhabdomyosarcoma	157	27 (17.2)	0.92 (0.57, 1.47)	0.92 (0.57, 1.47)
Wilms	238	43 (18.1)	0.92 (0.62, 1.37)	0.92 (0.62, 1.37)
Bone tumors	316	53 (16.8)	1.02 (0.74, 1.41)	1.01 (0.73, 1.40)
Germcell tumors	429	72 (16.8)	0.93 (0.70, 1.24)	0.93 (0.70, 1.23)
Melanoma	208	42 (20.2)	1.23 (0.84, 1.80)	1.23 (0.84, 1.79)
Health care professionals				
Controls	169253	17868 (10.5)	Ref.	Ref.
ALL	1191	130 (10.9)	1.06 (0.87, 1.29)	1.05 (0.86, 1.28)
Medulloblastoma	174	28 (16.1)	1.69 (1.09, 2.63)	1.71 (1.10, 2.66)
Retinoblastoma	130	19 (14.6)	1.53 (0.90, 2.63)	1.55 (0.91, 2.66)
Melanoma	196	30 (15.3)	1.54 (1.01, 2.33)	1.52 (1.00, 2.30)
Non-health care professionals				
Controls	165743	14358 (8.7)	Ref.	Ref.
ALL	1175	114 (9.7)	1.23 (0.97, 1.56)	1.24 (0.98, 1.58)
Medulloblastoma	170	24 (14.1)	2.04 (1.23, 3.39)	2.02 (1.22, 3.36)
Retinoblastoma	120	9 (7.5)	0.86 (0.35, 2.15)	0.81 (0.45, 1.46)
Melanoma	178	12 (6.7)	0.68 (0.31, 1.46)	0.90 (0.57, 1.40)

[a]Adjusted for maternal age, matching factors (i.e., birth year, sex).

Note: In the subgroup analysis, offspring whose mothers were healthcare professionals exposed to any heavy OPA were compared with offspring whose mothers were unexposed to any heavy OPA. Similarly, offspring whose mothers were non-healthcare professionals exposed to any heavy OPA were compared with offspring whose mothers were unexposed to any heavy OPA.

Table 3.3 Odds ratios (95% confidence intervals) for childhood cancers and OPA intensity (P*L) during pregnancy, 1968-2013

OPA Intensity	**N (%)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**	
Controls				
No exposure	151385 (82.5)	Ref.	Ref.	
Low (0-25%)	5518 (3.0)	Ref.	Ref.	
Medium (25-75%)	18575 (10.1)	Ref.	Ref.	
High (>75%)	8133 (4.4)	Ref.	Ref.	
ALL				
No exposure	1061 (81.3)	Ref.	Ref.	
Low (0-25%)	40 (3.1)	1.00 (0.66, 1.50)	1.00 (0.67, 1.51)	
Medium (25-75%)	139 (10.7)	1.07 (0.88, 1.30)	1.06 (0.87, 1.29)	
High (>75%)	65 (5.0)	1.36 (1.00, 1.85)	1.38 (1.02, 1.87)	P for trend = 0.23
Medulloblastoma				
No exposure	146 (73.7)	Ref.	Ref.	
Low (0-25%)	9 (4.6)	2.00 (0.92, 4.31)	1.99 (0.92, 4.30)	
Medium (25-75%)	27 (13.6)	1.60 (1.02, 2.50)	1.61 (1.03, 2.53)	
High (>75%)	16 (8.1)	2.49 (1.36, 4.56)	2.47 (1.35, 4.52)	P for trend < 0.01
Melanoma				
No exposure	166 (79.8)	Ref.	Ref.	
Low (0-25%)	6 (2.9)	0.98 (0.36, 2.66)	0.99 (0.36, 2.68)	
Medium (25-75%)	30 (14.4)	1.49 (0.98, 2.25)	1.47 (0.97, 2.23)	
High (>75%)	6 (2.9)	0.54 (0.17, 1.69)	0.54 (0.17, 1.71)	P for trend = 0.51

[a]Adjusted for maternal age, and matching factors (i.e., birth year, sex).

3.5 Discussion

Our nationwide register-based study is the first to estimate an association between maternal OPA and childhood cancer risks. We observed that heavy maternal OPA exposure is associated with increased risks for medulloblastoma in offspring. There are limited studies on maternal occupational exposures in relation to medulloblastoma, and changes in pathologic classifications make it difficult to compare to previous studies. Several maternal occupations with potentially heavy OPA increased the risk of medulloblastoma, including pig and chicken farming, employment as an electrician, and employment in agriculture.[59,62] Each of these maternal occupations also appeared in the JEM of heavy OPA applied in the present study. An increase in melanoma with heavy maternal OPA was found solely in the offspring of health care professionals, and not in non-health care professionals or after exclusion of correlated occupational exposures; therefore, our results for melanoma are likely chance findings in a subgroup analysis only. In addition, a dose response analysis could not confirm the positive association observed in healthcare professionals.

During the period of this study, Danish women were entitled to up to 4 weeks of maternity leave prior to giving birth. Thus, the results we observed should be interpreted as reflecting the effects of heavy OPA in the first and second trimesters.[184] Moreover, Danish employers are legally obligated to modify work tasks to meet the needs of pregnant women,[184] and further, women may have earlier maternity leave if working conditions require high physical demands.[185] Thus, work tasks that involve manual labor can be reduced, and this would have decreased the actual level of OPA experienced by women during pregnancy.

Medulloblastoma, one of the most common malignant brain tumors and embryonal tumors in children, arises from immature precursors of cerebellar granule neurons. Several biological mechanisms may explain the associations we observed. In the present study, viral infections are more frequent in the occupations that have a high physical demand (e.g., police and the judicial system and healthcare) consistent with previous findings that occupations requiring heavy OPA are at a higher risk of infections.[186] Moreover, physical activity is among the factors which determine viral spread in the central nervous system.[187] Perinatal expression of IFN- γ (an antiviral mediator of eliminating virus) in the central nervous system upregulates the sonic hedgehog signaling pathway and was specifically implicated in medulloblastoma tumor initiation in a mouse model.[188] Thus, pregnancy OPA might cause or moderate the IFN-γ induction by viral infection of the cerebellum which contributes to medulloblastoma in offspring, however this hypothesis remains to be more fully investigated. In the present study, adjustment for viral infections resulting in hospitalization did not change results, however common infections that do not cause women to seek healthcare may be underreported in our data source.[189]

Alternatively, high OPA may also be causing use of pain medications.[183] Although we did not observe differences in prescription drug use during pregnancy by exposure status, pregnancy OPA that increases musculoskeletal aches,[190] may result in higher use of over the counter pain relievers for which we have no records.[191] In Northern Europe, compared to non-healthcare providers, healthcare providers were 42% more likely to use over the counter medications of which acetaminophen accounts for over 60%, mostly for pain conditions during pregnancy.[183] A high prevalence of over the counter pain reliever use among nurses and physicians was also seen

in the US.[192] Studies in which medication use was assessed by a combination of self-report and records found that the use of analgesics or acetaminophen specifically increased the risk of childhood cancers combined (risk ratio=1.38, $p < 0.01$) [193] and possibly also the risk of brain tumors in offspring but only 8 cases were exposed and the confidence interval was very wide (adjusted OR=1.7, 95% CI: 0.6-5.4).[194] Evidence for acetaminophen's neurotoxicity in pregnancy is increasing but it is not known whether it impacts medulloblastoma.[195,196]

Occupational activities such as long hours of standing and heavy lifting increase the risk of prematurity and low birth weight of infants.[197-199] Physically demanding work can decrease uterine blood flow and nutrients availability such as carbohydrates, increase contractility of the uterus, and cause hyperthermia and high energy expenditure. These factors potentially alter fetal growth and development [200-202] which can further affect the risk of childhood cancer. The risk of medulloblastoma has been associated with fetal growth.[174] However, the lack of association of maternal heavy OPA with cancers related to low birth weight including AML and neuroblastoma [173,176] suggests that maternal heavy OPA may not affect childhood cancer risk through this biologic pathway.

There are several limitations of the study. LTPA is not available in our study. Persons working in higher-OPA positions tend to have lower levels of leisure-time physical activity [203] which was suggested to have beneficial effects for mothers and offspring,[48] although it has not been linked to decreased childhood cancer risk. We did not have information on psychosocial work-related factors including social support from co-workers or supervisors, stress from work deadlines, and mental strain at work which have been related to higher OPA.[204] However, none of these factors

are risk factors for childhood cancer. In addition, a potential for exposure misclassification arises from assigning exposures using a JEM.

This study has several strengths. We used a nationwide and validated register to identify childhood cancer cases to reduce the risk of case misclassification and avoid selection bias. Also, we used validated registers to identify maternal employment histories.

3.6 Conclusions

Overall, our findings suggest that heavy maternal OPA during pregnancy is associated with medulloblastoma in offspring. The National Institute for Occupational Safety and Health recommends that pregnant women reduce the amount of high physical workload including lifting, standing, and bending which may increase the risk of miscarriage, preterm birth, and menstrual disorders. If the observed associations are corroborated and not due to other work-place factors related to heavy OPA such as a high risk of infections, this would suggest the need to implement stricter employment regulations to protect pregnant women from high levels of physical activity at work.

3.7 Appendix

Table S3.1 Prevalence of occupations included in the OPA job-exposure matrix, stratified by case/control status, 1968–2013

Rank	Job codes	Occupation title	All subjects		Cases		Controls	
			N	%	N	%	N	%
1	93311	Hospitals, sanatoriums and similar health institutions	18583	9.8	731	10.3	17852	9.7
2	72002	Telegraph and telephone services	828	0.4	31	0.4	797	0.4
3	31142	Production of canned fish, fish forcemeat and fish filets	760	0.4	24	0.3	736	0.4
4	33201	Wooden and upholstered furniture factories	721	0.4	24	0.3	697	0.4
5	93406	Welfare institutions and societies	696	0.4	20	0.3	676	0.4
6	50121	General contracting businesses	561	0.3	16	0.2	545	0.3
7	35609	Other manufacture of plastic goods	538	0.3	22	0.3	516	0.3
8	38299	Manufacture of other machinery	512	0.3	19	0.3	493	0.3
9	91020	Police and the judicial system	504	0.3	15	0.2	489	0.3
10	34240	Daily papers	449	0.2	8	0.1	441	0.2

Note: Only the top 10 most commonly reported occupations during pregnancy are shown.

Table S3.2 Maternal OPA during pregnancy and childhood cancer risk, excluding women who had occupational exposures correlated with pregnancy OPA[a], 1968-2013

Cancer type	Total	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Controls	158450	7316 (4.6)	Ref.	Ref.
All cancers	6068	252 (4.2)	0.86 (0.73, 1.01)	0.86 (0.73, 1.01)
ALL	1111	51 (4.6)	0.99 (0.70, 1.42)	1.00 (0.70, 1.43)
AML	240	21 (8.8)	1.61 (0.84, 3.07)	1.63 (0.85, 3.11)
Hodgkin	349	16 (4.6)	0.88 (0.47, 1.66)	0.89 (0.47, 1.69)
NHL	111	5 (4.5)	0.37 (0.05, 2.71)	0.38 (0.05, 2.74)
CNS	1468	49 (3.3)	0.78 (0.56, 1.10)	0.78 (0.56, 1.10)
Gliomas	765	24 (3.1)	0.81 (0.52, 1.27)	0.80 (0.51, 1.26)
Medulloblastoma	156	11 (7.1)	1.91 (0.99, 3.80)	1.89 (0.98, 3.77)
Neuroblastoma	244	6 (2.5)	0.50 (0.19, 1.36)	0.51 (0.19, 1.39)
Retinoblastoma	115	<5	0.33 (0.05, 2.35)	0.32 (0.04, 2.33)
Rhabdomyosarcoma	133	<5	------	------
Wilms	207	12 (5.8)	------	------
Bone tumors	270	7 (2.6)	0.81 (0.38, 1.72)	0.82 (0.38, 1.74)
Germcell tumors	375	18 (4.8)	0.87 (0.48, 1.60)	0.88 (0.48, 1.61)
Melanoma	170	5 (2.9)	0.56 (0.18, 1.76)	0.56 (0.18, 1.77)

[a]Occupational exposures that were correlated with maternal OPA during pregnancy were excluded (i.e., welding fumes, iron, methylene chloride, sulfur dioxide, chromium, night shift work, gasoline and nickel).

[b]Adjusted for maternal age, matching factors (i.e., birth year, sex).

Table S3.3 Maternal OPA during pregnancy and childhood cancer risk, stratifying by healthcare and non-healthcare professionals, 1968-2013

Cancer type	Total	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Health care professionals				
Controls	169229	17844 (10.5)	Ref.	Ref.
All cancers	6556	731 (11.2)	1.05 (0.97, 1.14)	1.05 (0.96, 1.14)
ALL	1191	130 (10.9)	1.06 (0.87, 1.29)	1.05 (0.86, 1.28)
AML	249	29 (11.7)	1.30 (0.86, 1.96)	1.28 (0.84, 1.93)
Hodgkin	376	43 (11.4)	0.96 (0.67, 1.36)	0.94 (0.66, 1.34)
NHL	117	11 (9.4)	0.77 (0.39, 1.52)	0.78 (0.39, 1.53)
CNS	1603	181 (11.3)	1.03 (0.87, 1.22)	1.03 (0.87, 1.22)
Gliomas	840	98 (11.7)	1.06 (0.84, 1.33)	1.07 (0.85, 1.35)
Medulloblastoma	174	28 (16.1)	1.69 (1.09, 2.63)	1.71 (1.10, 2.66)
Neuroblastoma	263	25 (9.5)	0.87 (0.56, 1.34)	0.85 (0.55, 1.32)
Retinoblastoma	130	19 (14.6)	1.53 (0.90, 2.63)	1.55 (0.91, 2.66)
Rhabdomyosarcoma	147	17 (11.6)	1.01 (0.59, 1.73)	1.01 (0.59, 1.73)
Wilms	221	26 (11.8)	1.11 (0.72, 1.73)	1.12 (0.72, 1.75)
Bone tumors	297	34 (11.5)	1.01 (0.68, 1.48)	1.00 (0.68, 1.47)
Germcell tumors	398	41 (10.3)	0.96 (0.68, 1.35)	0.95 (0.67, 1.33)
Melanoma	196	30 (15.3)	1.54 (1.01, 2.33)	1.52 (1.00, 2.30)
Non-health care professionals				
Controls	165743	14358 (8.7)	Ref.	Ref.
All cancers	6346	521 (8.2)	0.97 (0.87, 1.09)	0.98 (0.87, 1.09)
ALL	1175	114 (9.7)	1.23 (0.97, 1.56)	1.24 (0.98, 1.58)
AML	251	31 (12.4)	1.43 (0.86, 2.37)	1.44 (0.87, 2.40)
Hodgkin	360	27 (7.5)	0.79 (0.48, 1.30)	0.80 (0.49, 1.31)

NHL	117	11 (9.4)	0.44 (0.11, 1.80)	0.44 (0.11, 1.81)
CNS	1537	115 (7.5)	0.97 (0.77, 1.22)	0.97 (0.77, 1.21)
Gliomas	808	66 (8.2)	1.09 (0.81, 1.45)	1.08 (0.81, 1.45)
Medulloblastoma	170	24 (14.1)	2.04 (1.23, 3.39)	2.02 (1.22, 3.36)
Neuroblastoma	260	22 (8.5)	0.79 (0.44, 1.43)	0.99 (0.74, 1.32)
Retinoblastoma	120	9 (7.5)	0.86 (0.35, 2.15)	0.81 (0.45, 1.46)
Rhabdomyosarcoma	140	10 (7.1)	0.73 (0.32, 1.68)	0.86 (0.34, 2.13)
Wilms	212	17 (8.0)	0.59 (0.27, 1.26)	0.73 (0.32, 1.68)
Bone tumors	282	19 (6.7)	1.03 (0.63, 1.70)	0.59 (0.27, 1.25)
Germcell tumors	388	31 (8.0)	0.89 (0.57, 1.39)	1.05 (0.63, 1.73)
Melanoma	178	12 (6.7)	0.68 (0.31, 1.46)	0.90 (0.57, 1.40)

[a]Adjusted for maternal age, matching factors (i.e., birth year, sex).

Note: In the subgroup analysis, offspring whose mothers were healthcare professionals exposed to any heavy OPA were compared with offspring whose mothers were unexposed to any heavy OPA. Similarly, offspring whose mothers were non-healthcare professionals exposed to any heavy OPA were compared with offspring whose mothers were unexposed to any heavy OPA.

Table S3.4 Odds ratios (95% confidence intervals) for childhood cancers and intensity of OPA (P*L) during pregnancy, 1968-2013

	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Controls			
No exposure	151385 (82.5)	Ref.	Ref.
Low (0-25%)	5518 (3.0)	Ref.	Ref.
Medium (25-75%)	18575 (10.1)	Ref.	Ref.
High (>75%)	8133 (4.4)	Ref.	Ref.
All cancers			
No exposure	5825 (82.3)	Ref.	Ref.
Low (0-25%)	193 (2.7)	0.92 (0.77, 1.10)	0.92 (0.77, 1.10)
Medium (25-75%)	761 (10.8)	1.05 (0.96, 1.14)	1.04 (0.96, 1.13)
High (>75%)	298 (4.2)	1.01 (0.87, 1.17)	1.01 (0.87, 1.18)
ALL			
No exposure	1061 (81.3)	Ref.	Ref.
Low (0-25%)	40 (3.1)	1.00 (0.66, 1.50)	1.00 (0.67, 1.51)
Medium (25-75%)	139 (10.7)	1.07 (0.88, 1.30)	1.06 (0.87, 1.29)
High (>75%)	65 (5.0)	1.36 (1.00, 1.85)	1.38 (1.02, 1.87)
AML			
No exposure	220 (78.6)	Ref.	Ref.
Low (0-25%)	10 (3.6)	1.28 (0.56, 2.90)	1.28 (0.57, 2.92)
Medium (25-75%)	32 (11.4)	1.27 (0.85, 1.92)	1.26 (0.84, 1.89)
High (>75%)	18 (6.4)	1.55 (0.81, 2.96)	1.58 (0.83, 3.01)
Hodgkin			

No exposure	333 (82.6)	Ref.	Ref.
Low (0-25%)	10 (2.5)	0.95 (0.47, 1.92)	0.95 (0.47, 1.93)
Medium (25-75%)	47 (11.7)	0.98 (0.69, 1.38)	0.96 (0.68, 1.36)
High (>75%)	13 (3.2)	0.60 (0.28, 1.28)	0.61 (0.29, 1.30)
NHL			
No exposure	106 (82.8)	Ref.	Ref.
Low (0-25%)	<5	------	------
Medium (25-75%)	12 (9.4)	0.72 (0.37, 1.43)	0.74 (0.37, 1.45)
High (>75%)	7 (5.5)	0.47 (0.06, 3.41)	0.47 (0.07, 3.43)
CNS			
No exposure	1422 (82.8)	Ref.	Ref.
Low (0-25%)	45 (2.6)	0.99 (0.70, 1.40)	0.99 (0.70, 1.40)
Medium (25-75%)	180 (10.5)	0.98 (0.83, 1.17)	0.98 (0.83, 1.17)
High (>75%)	71 (4.1)	1.11 (0.84, 1.48)	1.11 (0.84, 1.48)
Gliomas			
No exposure	742 (81.9)	Ref.	Ref.
Low (0-25%)	26 (2.9)	0.97 (0.60, 1.55)	0.97 (0.60, 1.55)
Medium (25-75%)	99 (10.9)	1.03 (0.82, 1.30)	1.04 (0.83, 1.30)
High (>75%)	39 (4.3)	1.29 (0.91, 1.84)	1.28 (0.90, 1.83)
Medulloblastoma			
No exposure	146 (73.7)	Ref.	Ref.
Low (0-25%)	9 (4.6)	2.00 (0.92, 4.31)	1.99 (0.92, 4.30)
Medium (25-75%)	27 (13.6)	1.60 (1.02, 2.50)	1.61 (1.03, 2.53)
High (>75%)	16 (8.1)	2.49 (1.36, 4.56)	2.47 (1.35, 4.52)

Neuroblastoma			
No exposure	238 (83.5)	Ref.	Ref.
Low (0-25%)	9 (3.2)	0.84 (0.34, 2.05)	0.84 (0.35, 2.06)
Medium (25-75%)	27 (9.5)	0.91 (0.60, 1.38)	0.89 (0.59, 1.36)
High (>75%)	11 (3.9)	0.61 (0.25, 1.49)	0.62 (0.26, 1.52)
Retinoblastoma			
No exposure	111 (79.9)	Ref.	Ref.
Low (0-25%)	<5	-----	-----
Medium (25-75%)	20 (14.4)	1.58 (0.93, 2.68)	1.60 (0.94, 2.71)
High (>75%)	5 (3.6)	0.97 (0.30, 3.10)	0.96 (0.30, 3.07)
Rhabdosarcoma			
No exposure	130 (82.8)	Ref.	Ref.
Low (0-25%)	5 (3.2)	0.63 (0.15, 2.55)	0.63 (0.15, 2.55)
Medium (25-75%)	17 (10.8)	0.98 (0.57, 1.68)	0.98 (0.57, 1.68)
High (>75%)	5 (3.2)	0.91 (0.33, 2.48)	0.91 (0.33, 2.49)
Wilms tumors			
No exposure	195 (81.9)	ref	ref
Low (0-25%)	7 (2.9)	0.64 (0.20, 2.00)	0.64 (0.20, 2.00)
Medium (25-75%)	26 (10.9)	1.07 (0.69, 1.66)	1.08 (0.69, 1.68)
High (>75%)	10 (4.2)	0.62 (0.23, 1.67)	0.61 (0.23, 1.66)
Bone tumors			
No exposure	263 (83.2)	Ref.	Ref.
Low (0-25%)	8 (2.5)	1.08 (0.51, 2.31)	1.09 (0.51, 2.32)
Medium (25-75%)	37 (11.7)	1.10 (0.76, 1.59)	1.09 (0.75, 1.58)

High (>75%)	8 (2.5)	0.68 (0.30, 1.53)	0.69 (0.30, 1.55)
Germcell			
No exposure	357 (83.2)	Ref.	Ref.
Low (0-25%)	7 (1.6)	0.43 (0.16, 1.15)	0.43 (0.16, 1.15)
Medium (25-75%)	44 (10.3)	1.00 (0.72, 1.39)	0.99 (0.71, 1.38)
High (>75%)	21 (4.9)	1.09 (0.63, 1.87)	1.10 (0.64, 1.88)
Melanoma			
No exposure	166 (79.8)	Ref.	Ref.
Low (0-25%)	6 (2.9)	0.98 (0.36, 2.66)	0.99 (0.36, 2.68)
Medium (25-75%)	30 (14.4)	1.49 (0.98, 2.25)	1.47 (0.97, 2.23)
High (>75%)	6 (2.9)	0.54 (0.17, 1.69)	0.54 (0.17, 1.71)

[a]Adjusted for maternal age, matching factors (i.e., birth year, sex).

Chapter 4. Child serum metabolome and maternal birthplace among Hispanics

4.1 Abstract

Background: Differences in gestational factors, health-related behaviors, psychosocial and environmental stressors in pregnancy have been proposed as explanations for the favorable reproductive outcomes among immigrant compared to US-born women of Hispanic ethnicity. Whether differences in risk by maternal nativity are also reflected in the newborn metabolome is unknown. Therefore, we investigated metabolic profiles in newborns of foreign-born and US-born Hispanic women.

Methods: We retrieved neonatal dried blood spots for 409 children born in California from 1983 to 2011 whose mothers were either US-born or foreign-born Hispanic as recorded on birth certificate (US-born: n=135; foreign-born: n=274). Liquid chromatography-high resolution mass spectrometry was used to generate metabolic profiles in an untargeted manner. Partial least squares discriminant analysis (PL-SDA) and pathway analyses were conducted to identify metabolic features and biologic pathways associated with maternal nativity.

Results: In total, 10,888 metabolic features were extracted from hydrophilic interaction chromatography and 7,271 metabolic features were extracted from C18 reverse phase columns. PL-SDA identified 917 discriminative features as being associated with maternal nativity. Pathway analysis identified 8 enriched pathways indicative of alterations in oxidative stress and inflammatory pathways (i.e., tryptophan, arginine and proline, aspartate and asparagine, tyrosine, linoleate, methionine and cysteine metabolism), energy production related pathways (i.e., carnitine shuttle) as well as xenobiotics metabolism based on the neonate's metabolome independent of maternal age, maternal urban/rural area of residence, delivery methods, parity,

prenatal care, smoking at the time of birth, infant's birth weight, infant's sex, and preterm birth status.

Conclusions: After controlling for known sources of difference in the neonate's metabolome, metabolic profiles of newborns of US-born compared to foreign-born Hispanic mothers differed in multiple pathways, most importantly in those related to inflammation and oxidative stress.

4.2 Introduction

Despite disparities in health care access and socioeconomic status, previous studies reported favorable birth outcomes (e.g., preterm birth, low birth weight) and childhood health among children of Hispanic immigrant women.[77,81,205] This phenomenon is often termed the "Hispanic epidemiologic paradox". In studies that investigated disparities in birth outcomes by maternal nativity in Hispanics, foreign-born Hispanic mothers consumed more nutritious diets and less fast food per day,[88,90,91] were less likely to smoke or consume alcohol,[89] were more likely to initiate and continue breastfeeding,[93] were more likely to have supportive social environments,[97] but were also more likely to live closer (<500m distance) to primary highways or roads.[94] Children of foreign-born Hispanic mothers tend to have a lower risk of asthma and obesity,[206,207] although health advantages tend to fade as children get older.[208] Immigrants are more likely to reside in more polluted areas with higher concentrations of traffic-related air pollution and PM2.5.[209,210] Given that prenatal exposure to traffic-related air pollution increases the risk of low birth weight,[211] birth outcomes among Hispanic immigrant mothers would be expected to be compromised by higher exposure to air pollution.

Although some evidence exists that maternal health behavior and psychosocial factors are related to health advantages of infants and children of foreign-born Hispanic mothers, relatively little is known whether there are measurable metabolic differences in the neonates that may reflect both maternal characteristics and environmental exposures as there are few reports concerning the influence of nativity on serum metabolites in pregnancy.[102,103] Here, we rely on data generated in an untargeted metabolomics study using archived newborn dried blood spots to identify

biologically relevant pathways and small molecules associated with maternal nativity among Hispanics.

4.3 Methods

The data in this study originate from a case-control study of childhood cancer in California in which controls were frequency matched to cases by birth year,[139] and all children were born between 1983 and 2011. We included in the current analysis only control children who were cancer free, born at a gestational age between 21 and 46 weeks with a recorded birth weight ≥500g and having a mother who was of US-born or foreign-born Hispanic ethnicity as recorded on the birth certificate. Mothers with diabetes (n=7) or preeclampsia (n=8) were excluded because disorder specific alterations in serum metabolites are expected,[212] leaving a total of 409 children. Admission to the newborn intensive care unit was only reported on birth certificates starting in 2006, but none of the newborns in our study had been admitted to the intensive care unit among those born after that year. After excluding 3 samples of children because of missing covariates, we retained data from 406 dried blood spot samples for our adjusted models. Maternal birthplace and Hispanic origin were self-reported and provided on birth certificate allowing us to distinguish US-born and foreign-born Hispanic women.

Dried blood spots of all eligible children were collected on Schleicher and Schuell Specimen Collection Paper by the California Genetic Disease Screening Program. Since 1982, dried blood spots were collected between 12 hours and 6 days after birth for the state mandated genetic and metabolic disorder screening of neonates. After the required testing was completed, the remaining specimen were stored at −20°C in the California biobank freezers. Additional details

of dried blood specimen collection and storage are described elsewhere.[213] All information on covariates was obtained from birth certificates except maternal smoking close to the time of birth which was identified by detection of cotinine in dried blood spots, and traffic related air pollution which was estimated by employing the CALINE4 model for all birth years after 1997 that had maternal residential address information.[214] Given that maternal smoking on the birth certificate (starting in 1991) is underreported and cotinine is a well-established biomarker of smoking, we identified mothers who smoked close to the time of birth by detection of cotinine (yes/no) in dried blood spots of neonates.

Dried blood spot samples were punched using a 5mm hole puncher and treated with 2:1 acetonitrile in water (containing a mixture of stable isotopic internal standards). Samples were mixed for 12 hours at 0-4 °C in the dark and then centrifuged to remove particulate matter. Neonatal blood spot samples were randomized and run in batches of 40, with pooled reference plasma (Q-Standard) samples analyzed prior to and following each batch, and NIST 1950 run at the beginning and end of the study to enable quality control. Samples were analyzed in triplicate using liquid chromatography with ultra-high resolution mass spectrometry (LC-HRMS; Fusion, Thermo Scientific). We used both positive electrospray ionization mode spectrometry with HILIC columns and negative electrospray ionization mode spectrometry with C18 reverse phase columns. The mass to charge ratio (*m/z*) obtained ranged from 85-1275. Peak extraction and quantification of ion intensities were conducted using *apLCMS* [215] and *xMSanalyzer*,[216] followed by batch correction with *ComBat*.[217] Metabolic feature tables based on the analyses described above contained accurate *m/z*, retention time, and relative ion intensity for *m/z* features across all samples.

Intensities of three replicates of each feature were summarized by the median. When 2 or more than 2 of the replicates were missing, the value was set to missing. Metabolic features detected in > 70% of overall blood spot samples, with a median coefficient of variation (CV) < 30% and Pearson correlation > 0.7 were retained for further analyses. Missing values were imputed using half of the lowest signal detected for a feature across all samples. Intensities were log2 transformed before analyses.

We generated residuals of intensities derived from linear regression. We adjusted for birth year as it indicates storage time for the blood spots and may reflect some degree of sample deterioration over time. To account for some of the potential sources of the neonatal metabolomic profile differences by maternal nativity, we controlled for well-known demographic and pregnancy-related factors that may be associated with newborn metabolomic profiles.[102,218-221] Thus, we adjusted for maternal age, urban/rural area of residence, prenatal care (began in 1st trimester, no care or began after 1st trimester), birth weight category (2499 g or less, 2500-3999 g, 4000+ g), infant's sex, delivery methods (vaginal, Cesarean), parity (0,1, ≥2), preterm birth status (37 weeks or less, 37+ weeks) and detection of cotinine (yes/no). We derived the residuals from this adjusted model.

We performed PL-SDA to identify features associated with maternal nativity. Variable importance in the projection (VIP) scores ≥2 was used to discriminate between features that were substantially related to maternal birthplace. Fold change was calculated as the ratio of raw intensities between newborns of foreign-born and US-born Hispanic mothers.

Maternal birthplace-related metabolic features were first matched to authenticated chemical standards (identification confidence level 1) analyzed using LC-MS/MS with an accurate mass threshold of 5 parts-per-million (ppm) and retention time error of 15s. To identify additional metabolic features, *xMSannotator* was used to match the *m/z* to the Human Metabolome Database (HMDB), with a mass error threshold of 10 ppm.[222]

Pathway enrichment analysis was conducted through *Mummichog* using features with VIP scores ≥ 2 to identify metabolic pathways related to maternal nativity. By mapping metabolic features to known biologic pathways, the most likely match was detected for certain metabolites. To reduce false positive discovery, metabolites tentatively annotated by *Mummichog* required the presence of the primary adducts (M+H for positive and M-H for negative ion mode). Enriched pathways were retained for further interpretation if they contained three or more overlapping metabolites per pathway. An adjusted p for each pathway was calculated through resampling by *Mummichog* based on a gamma distribution which assigns greater significance to pathways with more reference hits. The P-value threshold we used was 0.05.

We conducted several sensitivity analyses. To detect metabolic pathways related to gestational age and birth weight, we restricted to term birth with birthweight ≥ 2500g (n=366) and compared the results with those using everyone. In addition, we adjusted in sensitivity analyses for variables that were not available during the entire study period including source of payment for prenatal care (starting in 1989; private/Health Maintenance Organization (HMO)/Blue Cross Blue Shield (BCBS), MediCal/Government/self-pay), air pollution from traffic estimated by

CALINE4 (1998-2007). Because marital status was available only between 1998 and 2000, the small sample size (n=42) prevented adjustment for this factor. However, the percentages of married mothers are comparable between US-born and foreign-born mothers (66.7% vs 60.0%). To detect factors that are associated with metabolic differences in neonates and are also markers for maternal nativity, we compared the results before and after adjustment for these factors.

4.4 Results

The characteristics of the 409 study participants are presented in Table 4.1. Most mothers of neonates for whom we retrieved blood spots lived in urban areas. Compared to US-born Hispanic mothers and their offspring, foreign-born Hispanic mothers were older, had less education, and their children were less likely to be preterm birth and low birth weight.

We identified 15,597 features in HILIC column and 10,639 features in C18 column associated with maternal nativity. After filtering for missing values, 10,888 and 7,271 features remained in the HILIC column and C18 column, respectively. We identified 546 HILIC and 371 C18 metabolic features with VIP score ≥ 2. Among these significant features, we confirmed 20 metabolites using authentic standards (MSI level 1 criteria, Table 2). We conducted pathway enrichment analysis using *Mummichog* and identified 8 metabolic pathways associated with maternal birthplace at $p < 0.05$ (Tables 4.3). Tentative annotation results for metabolites from each pathway are presented in supplemental tables (Table S4.1.1 – S4.1.8).

We found perturbations in tryptophan, arginine, proline, aspartate and asparagine metabolism indicating associations between maternal nativity and inflammatory responses in newborns.

Disruption of tyrosine, linoleate, methionine and cysteine metabolism reflect changes in oxidative stress pathways. Carnitine shuttle pathway indicates changes in energy production. Finally, we also observed differences in xenobiotics metabolism.

Sensitivity analyses in which we restricted to term births with birthweight ≥ 2500g identified the same pathways except inflammation related pathways (i.e., tryptophan, arginine and proline, aspartate and asparagine metabolism; Table S4.2). With adjustment for source of payment for prenatal care, we saw no more differences in the pathways of squalene and cholesterol biosynthesis and the carnitine shuttle between infants born to foreign versus US born Hispanic mothers (Table S4.3.1-S4.3.2). When additionally adjusting for exposure to PM2.5 from traffic in the third trimester, all pathways except the linoleate metabolism were retained. On the other hand, were newly found the ascorbate and tyrosine metabolisms to be enriched in newborns of foreign-born mothers (Table S4.4.1 – S4.4.2).

Table 4.1 Characteristics of mothers and children by mother's ethnicity and birthplace (1983-2011)

Characteristics	US-born Hispanic (N=135)	Foreign-born Hispanic (N=274)
	N (%)	N (%)
Infant's sex		
Male	68 (50.4)	143 (52.2)
Female	67 (49.6)	131 (47.8)
Birth year		
1983-1989	11 (8.1)	39 (14.2)
1990-1996	35 (25.9)	82 (29.9)
1997-2003	32 (23.7)	77 (28.1)
2004-2011	57 (42.2)	76 (27.7)
Maternal age (years)		
19 or less	37 (27.4)	31 (11.3)
20-24	43 (31.9)	70 (25.5)
25-29	23 (17.0)	83 (30.3)
30-34	24 (17.8)	56 (20.4)
35 and older	8 (5.9)	34 (12.4)
Paternal age (years)		
19 or less	17 (14.2)	5 (1.9)
20-24	40 (33.3)	56 (21.8)
25-29	27 (22.5)	75 (29.2)
30-34	22 (18.3)	63 (24.5)
35-39	9 (7.5)	42 (16.3)
40+	5 (4.2)	16 (6.2)
Maternal education (years)		
8 or less years	0 (0)	85 (35.3)
9-11 years	44 (34.9)	74 (30.7)
12 years	53 (42.1)	56 (23.2)
13 to 15 years	18 (14.3)	18 (7.5)
16 more years	11 (8.7)	8 (3.3)
Paternal education (years)		
8 or less years	9 (8.3)	89 (38.9)
9-11 years	26 (23.9)	59 (25.8)
12 years	42 (38.5)	47 (20.5)
13 to 15 years	25 (22.9)	18 (7.9)
16 more years	7 (6.4)	16 (7.0)
Parity		
0	70 (51.9)	92 (33.7)
1	30 (22.2)	77 (28.2)
≥ 2	35 (25.8)	104 (38.0)

Preterm birth		
Yes	15 (11.1)	22 (8.0)
No	120 (88.9)	252 (92.0)
Birth weight		
2499 g or less	11 (8.1)	7 (2.6)
2500-3999	112 (83.0)	236 (86.4)
4000 +	12 (8.9)	30 (11.0)
Delivery methods		
Spontaneous/assisted vaginal	101 (74.8)	203 (74.1)
Primary/repeat/unspecified cesarean	34 (25.2)	71 (26.0)
Mother's residence		
Urban areas	129 (95.6)	262 (96.0)
Small town	3 (2.2)	6 (2.2)
Rural areas	3 (2.2)	5 (1.8)
Prenatal care visit		
Began in 1st trimester	109 (81.3)	205 (76.2)
No care or began after 1st trimester	25 (18.7)	64 (23.8)
Principal source of payment for prenatal care (1988+)		
Private	58 (46.4)	70 (28.8)
MediCal/Government/self-pay	67 (53.6)	173 (71.2)

Table 4.2 Confirmed[a] chemical identity of metabolic features in neonates associated with maternal nativity[b]

m/z	RT (s)	Adduct Form	Metabolite	Fold Change (Log2)	Column
101.0429	24.4	M-H[1-]	Acetoacetate	-0.42	c18neg
118.0507	22.5	M-H[1-]	Allothreonine	-0.24	c18neg
125.0179	21.3	M-H[1-]	4-imidazoleacetic acid	-2.94	c18neg
132.0125	21.2	M-H[1-]	D-ornithine	-0.59	c18neg
168.0708	25.8	M-H[1-]	Pyridoxine (Vitamin B6)	0.99	c18neg
219.0158	19.0	M-H[1-]	O-succinyl-l-homoserine	0.32	c18neg
226.0478	22.0	M-H[1-]	3-nitro-l-tyrosine	-0.76	c18neg
228.0818	21.3	M-H[1-]	D-ribose 5-phosphate	1.84	c18neg
328.1633	19.4	M-H[1-]	Adenosine 3',5'-cyclic monophosphate	-0.67	c18neg
482.1044	18.3	M-H[1-]	Uridine triphosphate	0.01	c18neg
579.0279	16.8	M-H[1-]	Uridine diphosphoglucuronic acid	0.74	c18neg
743.9467	36.5	M-H[1-]	Beta-nicotinamide adenine dinucleotide 2'-phosphate reduced (NADPH)	1.82	c18neg
103.0508	75.4	M+H[1+]	Cadaverine	0.04	HILICpos
136.55682	58.6	M+H[1+]	Homocysteine	-2.42	HILICpos
136.94026	44.9	M+H[1+]	Hypoxanthine	0.01	HILICpos
154.07391	53.6	M+H[1+]	Arabitol	-1.73	HILICpos
160.13319	31.6	M+H[1+]	Indole-3-acetaldehyde	0.11	HILICpos
219.12429	35.2	M+H[1+]	Pantothenic acid (Vitamin B5)	0.74	HILICpos

282.96345	27.2	M+H[1+]	Oleate	1.67	HILICpos
567.18229	36.9	M+H[1+]	1,2-didecanoyl-sn-glycero-3-phosphocholine	-1.05	HILICpos

[a]Chemical identification was conducted by matching peaks by accurate mass and retention time to authentic reference standards in an in-house library run under identical conditions using tandem mass spectrometry.

[b]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit, and detection of cotinine (yes/no).

Table 4.3 Enriched metabolomic pathways associated with maternal nativity[a]

Pathways	Overlap size	Pathway size	*p-value*	Mode
Tryptophan metabolism	5	40	0.0063	c18neg
Arginine and proline metabolism	3	21	0.01714	c18neg
Aspartate and asparagine metabolism	4	36	0.01874	c18neg
Xenobiotics metabolism	3	26	0.03084	c18neg
Methionine and cysteine metabolism	4	19	0.01176	HILICpos
Linoleate metabolism	4	20	0.01445	HILICpos
Carnitine shuttle	3	14	0.0237	HILICpos
Tyrosine metabolism	6	48	0.0379	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit and detection of cotinine (yes/no).

4.5 Discussion

In the present study, we found distinct patterns of metabolic features and pathways in newborn blood samples according to maternal nativity in Hispanics after controlling for known and measured factors that are expected to contribute to differences in neonate metabolome. Specifically, after controlling for birth year, birth weight, infant's sex, maternal age, urban/rural residential area, delivery methods, smoking (detection of cotinine in blood spot), preterm birth status, parity, and starting prenatal care early, maternal nativity was still associated with metabolites and pathways related to inflammatory responses and oxidative stress. During the years for which we were able to model traffic-related PM2.5 exposures based on residential addresses, only one oxidative stress related pathway (linoleate) was removed with adjustment for traffic-related PM2.5 exposure in late pregnancy. Our results suggest that there are additional maternal factors we were unable to measure that are associated with nativity in Hispanics and influence the neonatal metabolome in our study such as diet, stress, breastfeeding, and environmental exposures. Although differences in metabolite profiles by nativity have previously been noted in Hispanic adults,[102,103] no studies examined newborn metabolic profiles according to maternal nativity in Hispanics.

In the present study, we generally observed a downregulation in inflammation and oxidative stress in newborns of foreign-born Hispanic compared to US-born mothers. A maternal inflammatory response may induce an inflammatory response in the fetus either directly, by the passing of activated maternal lymphocytes [223] or maternally-produced cytokines [224,225] through the placenta into the fetal circulation; or indirectly, by inducing inflammation of the placenta, which in turn produces cytokines that are released into the fetal circulation. Hence, activation of

inflammation-related metabolic pathways in the newborn may reflect the inflammation status of the mother. The major pathway we linked to inflammation was tryptophan which is metabolized through the kynurenine pathway with a small amount being used for the biosynthesis of serotonin. In the present study, based on tentatively annotated metabolites, the kynurenine pathway was downregulated with lower levels of 5-hydroxy-N-formylkynurenine while the biosynthesis of serotonin was upregulated with 5-hydroxy-L-tryptophan (5-HTP) and 5-hydroxykynurenamine being higher in newborns of foreign-born Hispanic mothers. Indoleamine 2,3-dioxygenase (IDO), a key enzyme that catabolizes tryptophan in the kynurenine pathway, is activated by proinflammatory cytokines.[226] In addition, several metabolites in the kynurenine pathway are associated with oxidative stress.[227] The upregulation of 5-HTP in newborns of foreign-born Hispanic mothers is noteworthy because 5-HTP downregulates inflammation through the suppression of T cell activation and the production of proinflammatory cytokines.[228] Furthermore, levels of 5-methoxyindoleacetate (5-MIAA) - a metabolite formed during the biosynthesis of serotonin - were also found to be higher in newborns of foreign-born Hispanic mothers and it is thought to exhibit antioxidant properties.[229] Furthermore, a disruption in arginine, proline, aspartate and asparagine metabolism with citrulline being lower in newborns of Hispanic US-born mothers also suggested an upregulation in inflammatory responses.[230]

Our results indicating differences in inflammatory responses by nativity are consistent with previous findings using a different set of inflammatory biomarkers, for example, in a study that analyzed serum samples of non-pregnant Mexico-born women of reproductive age in the US, reported an increase in high levels of C-reactive protein (3.01–10.00 mg/L defined based on cardiometabolic risk) with increasing acculturation levels.[103] Another US study, focused on older

individuals (40 years+), also found foreign-born Hispanics to have lower levels of inflammatory markers (i.e., C-reactive protein and fibrinogen) compared to their US-born counterparts after controlling for socioeconomic status, health behaviors and access to care.[102] Known drivers of inflammatory reactions include preterm birth status and air pollution. In our study, restriction to term births with birth weight over 2500g removed inflammation related pathways (i.e., tryptophan, arginine, proline, aspartate and asparagine metabolism) which is in line with the evidence that preterm newborns experience sustained inflammation.[231] Interestingly, adjustment for PM2.5 exposure also changed metabolic responses related to oxidative stress and inflammation, i.e. removed the linoleate pathway that has previously been implicated in air pollution exposure in multiple studies [232,233] but not other oxidative stress related metabolites (i.e., nitrotyrosine, NADPH, homocysteine, cystathionine and L-DOPA) and pathways (i.e., tyrosine, methionine and cysteine metabolism). Before adjustment, the metabolites observed to be different between newborns of foreign-born and US-born Hispanic mothers were 13-hydroxy-9Z,11E-octadecadienoic acid (13-HODE) as well as γ-linolenic acid, the former one linked to oxidative stress and the later one an anti-inflammatory metabolite that inhibits the biosynthesis of the leukotriene B4. Previously, we examined metabolic responses to traffic-related air pollution in maternal mid-pregnancy serum samples and also found 13-HODE and γ-linolenic acid to be associated with air pollution exposures.[232] Neonates of foreign-born Hispanic mothers had experienced higher exposures to traffic related air pollution in late pregnancy; specifically, PM2.5 levels in the third trimester estimated by CALINE4 were slightly higher among foreign-born Hispanic mothers [mean (SD)= 0.91 (0.87) $\mu g/m^3$] compared to US-born Hispanic mothers [mean (SD)=0.87 (0.95) $\mu g/m^3$]. On the other hand, after adjustment for these CALINE4 measures that only represent traffic sources within 1200 meters of the mothers' residential

address at birth, the ascorbate and tyrosine pathways were newly implicated as distinguishing the two groups. The former is one of the most important anti-oxidants in serum while the later has been identified as a major air pollution related pathway in a human exposure chamber study,[234] suggesting that the neighborhoods of foreign-born and US Hispanics may still differ in terms of more regional sources of air pollution that we did not model.

The remaining variance in inflammatory responses and oxidative stress in neonates in our study might be explained by the unmeasured factors including healthy immigrant selection, healthier dietary patterns, lower rates of prepregnancy obesity, alcohol drinking, lower stress, lower rates of depression and less acculturation as these factors all have been reported to be different by maternal nativity and also been shown to possibly impact inflammatory responses,[103,235-240] and contribute to the production of free radicals or antioxidants.

Vitamin B6 was higher in newborns of foreign-born mothers. Vitamin B6 can cross the placenta from maternal compartments readily,[241] therefore, the higher levels in newborns may reflect higher levels in mothers. Our finding is consistent with prior observations that foreign-born women have a healthier diet in general, including being less likely to have vitamin B6 deficiency.[242] Our results suggest that the maternal diet affects the neonate's metabolome after adjustment for all variables we were able to include in our model.

We also found the carnitine shuttle to explain differences between Hispanic newborns of foreign-born and US-born mothers. Empirical compounds annotated in this pathway were three acylcarnitines (i.e., linoelaidyl carnitine, alpha-linolenyl carnitine, propionyl-carnitine) and they

were upregulated in newborns of foreign-born Hispanic mothers. Since the role of acylcarnitines is to transport organic and fatty acids into the mitochondria to be broken down to produce energy, an increased level of acylcarnitines might lead to an increase in energy production. The observed difference in the level of vitamin B5, a precursor of coenzyme A, also support the changes in energy metabolism according to maternal nativity. Acetoacetate, a ketone body, was lower in newborns of foreign-born Hispanic mothers. A previous study found that high ketone levels in newborn blood samples were associated with an inadequate breast milk intake in the early postnatal period.[243] In addition, the observed differences for hippurate may also point to breastfeeding practices. Hippurate in blood was found to be a biomarker for higher gut microbiome diversity.[244] Although multiple factors such as C-section alter the diversity of the gut microbiome in newborns, breastfeeding has been implicated as the main contributor.[245,246] In the present study, we did not see a difference for the percentages of C-section by maternal nativity groups. Collectively, the increase in ketone bodies and hippurate in newborns of US-born Hispanic mothers might suggest a lack of breastfeeding uptake which is in line with the finding that foreign-born Hispanic women historically have had higher rates of breastfeeding than US-born women.[247]

We are aware of several limitations of our study. First, we lacked measures of acculturation including the length of residence in the U.S. and the legal status of immigrant mothers. Second, as an intrinsic limitation of untargeted metabolomic analysis, we were only able to tentatively annotate the metabolites and intermediates without confirmation by tandem MS. However, the pathways inferred by Mummichog have been proven to reflect biological activity quite well.[248]

Third, current knowledge of the transport of nutrients and other metabolites between the maternal unit, placenta, and fetus is still limited.

4.6 Conclusions

Overall, our results indicate that maternal nativity may affect metabolic pathways in neonates related to oxidative stress and inflammation and also suggest some dietary and breastfeeding differences independent of many demographic and gestational factors and birth outcomes. The perturbations identified provide some biomarker-based insights into the disparities (air pollution) as well as resilience factors (diets, healthy behaviors, and breastfeeding practices) among Hispanics that may influence child health.

4.7 Appendix

Table S4.1.1 Methionine and cysteine metabolism using HILIC column with positive ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
106.0499	250.9	M+H[1+]	D-Serine	-2.48
88.03926	80.2	M+H[1+]	2-Aminoacrylate	-0.06
103.03969	44.6	M+H[1+]	Succinate semialdehyde	-0.07
223.07462	156.1	M+H[1+]	L-Cystathionine	0.84

Table S4.1.2 Tyrosine metabolism using HILIC column with positive ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
88.03926	80.2	M+H[1+]	2-Aminoacrylate	-0.06
180.06532	44.2	M+H[1+]	Hippurate	0.05
138.09137	175.8	M+H[1+]	Tyramine	-0.99
223.08272	47.3	M+H[1+]	Salsolinol 1-carboxylate	0.15
103.03969	44.6	M+H[1+]	Succinate semialdehyde	-0.07
198.07551	74.0	M+H[1+]	3,4-Dihydroxy-L-phenylalanine (L-DOPA)	-0.83

Table S4.1.3 Linoleate metabolism using HILIC column with positive ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
313.23716	22.9	M+H[1+]	(9Z,11E)-(13S)-13-Hydroperoxyoctadeca-9,11-dienoic acid (13-HODE)	-0.38
295.22659	23.1	M+H[1+]	CE5527	-0.13

155.10661	279.5	M+H[1+]	CE2577	-0.36
279.23167	23.9	M+H[1+]	(6Z,9Z,12Z)-Octadecatrienoic acid (γ-Linolenic acid)	-0.14

Table S4.1.4 Carnitine shuttle using HILIC column with positive ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
424.34215	21.5	M+H[1+]	Linoelaidyl carnitine	0.12
422.32551	21.3	M+H[1+]	Alpha-linolenyl carnitine	0.98
218.13857	31.0	M+H[1+]	Propionyl-carnitine	0.15

Table S4.1.5 Tryptophan metabolism using C18 column with negative ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
204.0672	23.1	M-H[1-]	5-Methoxyindoleacetate	0.8
179.0827	18.5	M-H[1-]	5-Hydroxykynurenamine	0.42
251.068	18.6	M-H[1-]	5-Hydroxy-N-formylkynurenine	-1.22
190.051	287.7	M-H[1-]	5-Phenyl-1,3-oxazinane-2,4-dione	0.15
219.0778	38.2	M-H[1-]	5-Hydroxy-L-tryptophan (5-HTP)	1.07

Table S4.1.6 Xenobiotics metabolism using C18 column with negative ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
579.0279	16.8	M-H[1-]	UDP-D-glucuronate	0.74

283.0738	36.8	M-H[1-]	9-Hydroxybenzo[a]pyrene-4,5-oxide	-1.41
170.9442	23.3	M-H[1-]	4-Bromophenol	-0.01

Table S4.1.7 Arginine and proline metabolism using C18 column with negative ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
114.0559	288.3	M-H[1-]	L-Proline	-0.01
144.0665	289.3	M-H[1-]	L-2-Aminoadipate 6-semialdehyde (Allysine)	-0.09
174.0872	21.9	M-H[1-]	L-Citrulline	0.12

Table S4.1.8 Aspartate and asparagine metabolism using C18 column with negative ion mode.

m/z	RT (s)	Adduct Form	Tentative Match	Fold change (log 2)
114.0559	288.3	M-H[1-]	L-Proline	-0.01
144.0665	289.3	M-H[1-]	L-2-Aminoadipate 6-semialdehyde	-0.09
174.0872	21.9	M-H[1-]	L-Citrulline	0.12
160.0252	17.8	M-H[1-]	N-formyl-L-aspartate	-0.33

Table S4.2 Enriched metabolomic pathways associated with maternal nativity[a], restricting to term birth with birthweight ≥ 2500g

Pathways	**Overlap size**	**Pathway size**	***p-value***	**Mode**
Xenobiotics metabolism	4	26	0.0179	c18neg
Ascorbate (Vitamin C) and aldarate metabolism	3	16	0.01983	c18neg
Squalene and cholesterol biosynthesis	3	11	0.00353	HILICpos
Methionine and cysteine metabolism	3	19	0.01521	HILICpos
Linoleate metabolism	3	20	0.01807	HILICpos
Carnitine shuttle	3	14	0.02563	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit and detection of cotinine (yes/no).

Table S4.3.1 Enriched metabolomic pathways associated with maternal nativity[a], 1989-2011

Pathways	Overlap size	Pathway size	*p-value*	Mode
Xenobiotics metabolism	4	26	0.01193	c18neg
Tryptophan metabolism	5	40	0.01412	c18neg
Linoleate metabolism	3	18	0.02134	c18neg
Methionine and cysteine metabolism	4	19	0.00924	HILICpos
Squalene and cholesterol biosynthesis	3	11	0.01218	HILICpos
Linoleate metabolism	4	20	0.01328	HILICpos
Carnitine shuttle	3	14	0.02101	HILICpos
Tyrosine metabolism	6	48	0.04151	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit and detection of cotinine (yes/no).

Table S4.3.2 Enriched metabolomic pathways associated with maternal nativity, with additional adjustment for source of prenatal care payment[a], 1989-2011

Pathways	Overlap size	Pathway size	*p-value*	Mode
Xenobiotics metabolism	4	26	0.02126	c18neg
Tryptophan metabolism	5	40	0.02605	c18neg
Linoleate metabolism	3	18	0.02891	c18neg
Tyrosine metabolism	6	60	0.04390	c18neg
Methionine and cysteine metabolism	4	19	0.00756	HILICpos
Linoleate metabolism	4	20	0.00865	HILICpos
Tyrosine metabolism	6	48	0.02756	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit, detection of cotinine (yes/no), source of prenatal care payment.

Table S4.4.1 Enriched metabolomic pathways associated with maternal nativity[a], 1998-2007

Pathways	Overlap size	Pathway size	*p-value*	Mode
Purine metabolism	6	40	0.00176	c18neg
Methionine and cysteine metabolism	4	27	0.0095	c18neg
Selenoamino acid metabolism	3	9	0.00453	HILICpos
Linoleate metabolism	4	20	0.0126	HILICpos
Pyrimidine metabolism	5	30	0.01487	HILICpos
Methionine and cysteine metabolism	3	18	0.04529	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit, and detection of cotinine (yes/no).

Table S4.4.2 Enriched metabolomic pathways associated with maternal nativity, with additional adjustment for PM2.5 in the third trimester[a], 1998-2007

Pathways	**Overlap size**	**Pathway size**	***p-value***	**Mode**
Ascorbate (Vitamin C) and aldarate metabolism	4	16	0.00034	c18neg
Purine metabolism	5	40	0.00286	c18neg
Methionine and cysteine metabolism	4	27	0.00319	c18neg
Pyrimidine metabolism	4	48	0.0241	c18neg
Selenoamino acid metabolism	3	9	0.00471	HILICpos
Pyrimidine metabolism	5	30	0.01202	HILICpos
Tyrosine metabolism	6	48	0.0321	HILICpos
Methionine and cysteine metabolism	3	18	0.04168	HILICpos

[a]Adjusted for birth year, birth weight (categorical), infant's sex, maternal age, urban/rural area of residence, delivery methods, preterm birth, parity, prenatal care visit, detection of cotinine (yes/no), and PM2.5 in the third trimester.

Chapter 5. Public health importance

Childhood cancer is a rare disease but remains the leading cause of death in western countries. Epidemiology studies identified few risk factors for childhood cancers accounting for a small number of cases. Other suspected risk factors are less established, and the effects vary across cancer types. The cumulative evidence would help us identify offspring at high risk and, consequently, issue or update prevention strategies recommendations. The public health relevance of the first two studies may fit into this frame. Our first study used two nationwide population-based samples of children born in Denmark and Taiwan to assess the impact of maternal diabetes on childhood cancer risk. In addition, we found strong evidence for an increased risk of central nervous system tumors in the offspring of diabetic mothers. Our findings underline the importance of prevention and management of diabetes during pregnancy. Our results are especially relevant given that women of childbearing age are at increased risk of pre-gestational and gestational diabetes internationally, driven in part by the increasing prevalence of obesity among pregnant women. Our second study found that heavy maternal occupational physical activity during pregnancy was associated with an increased risk of medulloblastoma and possibly melanoma in the offspring in Denmark. The positive association is noteworthy given that Denmark has one of the best parental benefits in the world. If associations are corroborated, regulations that aim to protect pregnant women from being exposed to high levels of physical activity at work should be considered. The physiological and psychological changes caused by pregnancy call for attention to have a closer examination of the recommendations of the type and the amount of physical activity that are truly beneficial to pregnant women and children.

The immigrant paradox has been noted in health outcomes in Hispanic children of foreign-born and US-born mothers. Given the continuously growing Hispanic population and high birth rate, it is crucial to understand declines in offspring health with increasing acculturation in this race/ethnic group. Our third study is the first to use blood samples of newborns to understand how maternal nativity operates to impact offspring health. With an untargeted approach, we can see a comprehensive picture of offspring metabolic profiles. Consistent with the literature on the immigrant paradox, maternal foreign-born nativity protects the health of Hispanic children. Changes in health behaviors and diet, social and economic inequalities that lead to declines in health outcomes across immigrant generations need to be addressed.

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