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Assessing risk factors for adverse birth outcomes and early childhood respiratory illness: an examination of supplement initiation and participation in Special Supplemental Nutrition Program for Women, Infants and Children during pregnancy

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

by

Vivian Helena Alfonso

2016

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ABSTRACT OF THE DISSERTATION

Assessing risk factors for adverse birth outcomes and early childhood respiratory illness: an examination of supplement initiation and participation in Special Supplemental Nutrition Program for Women, Infants and Children during pregnancy

by

Vivian Helena Alfonso

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2016

Professor Beate R. Ritz, Chair

In the United States, rate of preterm birth peaked in 2006 and little progress has been made to date despite ambitious Healthy People 2020 goals. Infants born premature are at higher risk of death and disability, including psychological conditions, learning difficulties and medical disabilities, than term newborns. Additionally, adverse birth outcomes are associated with asthma, the leading cause of chronic childhood illness and disability. According to the 'Barker hypothesis', intrauterine exposures may serve as a programming stimulus that alters the development of biologic systems and the risk or susceptibility to future disease. One such programming stimulus is maternal nutrition in pregnancy as previous research has shown associations between prenatal nutrition (such as vitamin supplement use and Special

Supplemental Nutrition Program for Women, Infants and Children enrollment (WIC)) and birth and early childhood respiratory health outcomes. Through this dissertation, we address gaps in knowledge regarding supplement use in pregnancy and prenatal enrollment in the nutrition program among low-income, minority women, allowing for better informed public health messages.

In the first study, we identified WIC eligible parous women who gave birth to first and second siblings between 2007 and 2011 from California electronic birth records to assess the impact of program enrollment on recurrent preterm birth. WIC eligibility in the second pregnancy was based upon both an income criteria (assessed through Medi-Cal as the second pregnancy primary payer for prenatal care) and "nutritional risk" (assessed through a premature first birth). We found that eligible second pregnancy non-enrollees had a higher risk of recurrent preterm birth than program participants among both first pregnancy WIC non-enrollees and first pregnancy WIC enrollees. These findings suggest that the benefits provided by WIC to patrons, including vouchers for food supplementation, counseling and referrals to health and social services, may improve birth outcomes of the women electing to enroll in the program. In sensitivity analyses, we also found the magnitude of this association was strongest for the following high risk subgroups of eligible women: first pregnancy Medi-Cal participants, younger, and Black or Hispanic mothers with the shortest time between births.

The second study used data from a Los Angeles based case-control study nested within the 2003 birth cohort to assess the relationship between the timing of pre-natal supplement initiation and birth outcomes. This study limited analyses to non-Hispanic white and Hispanic women, the predominant racial/ethnic groups among respondents. Among Hispanic mothers, we observed an increased odds of preterm birth the later a woman initiated pre-natal supplement use

in pregnancy and the magnitude of the association was larger in US-born compared to foreign-born women. The case-control respondents were followed approximately three years later to assess offspring respiratory outcomes. The third study objective was to assess whether adverse early childhood respiratory health is associated with the timing of folic acid supplement initiation in pregnancy. Among all study participants, timing of folic acid use (derived from reports of both folic acid and pre-natal supplements) was not associated with wheeze in the first three years of life, current wheeze, or lower respiratory tract infection in offspring even after re-weighing the population to account for premature birth and censorship. Among mothers with a history of eczema, hay fever or asthma, we found late folic acid supplement initiators had between 1.7-1.9 times the risk of adverse respiratory health outcomes compared to their first trimester initiating counterparts. No association was found among non-atopic mothers.

In conclusion, our results support that prenatal nutrition in pregnancy may serve as a programming stimulus as timing of supplement initiation and nutrition program enrollment were found to be associated with offspring health. Both are potentially modifiable factors and the information obtained through these studies highlights the importance of tailored public health interventions for those at highest risk of adverse birth and childhood respiratory health outcomes.

The dissertation of Vivian Helena Alfonso is approved.

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Chapter 1: Introduction and background

1.1 Fetal programming

The lifecourse perspective, first proposed as the 'Barker hypothesis', hypothesizes that the prenatal environment plays an integral role in the development of both adverse birth and early childhood health outcomes (Goldenberg & Culhane, 2007). They also posit more broadly that environmental influences experienced in early development, in particular during intrauterine life, result in permanent physiologic or pathologic changes that alter risk of disease throughout the lifespan (Barker & Osmond, 1986; Halfon et al, 2014). Intrauterine influences are believed to serve as a programming stimulus (Halfon & Hochstein, 2002; Halfon et al, 2014), which alters the development of biologic systems thus altering susceptibility to future disease (Barker et al, 1993). As fetal nutrition is a key regulator of fetal growth, it is a prime candidate for possible programming influence (Harding, 2001).

1.2 Offspring outcomes

1.2.1 Birth outcomes

Since 1981, there has been a 30% increase in the preterm birth (PTB) rate in the US (Davidoff et al, 2006). While the Healthy People 2010 preterm live birth target was set at 7.6%, a review of the nations' progress found the proportion increased from 11.6% in 2000 to 12.7% in 2007 (NCHS, 2012). After reaching the peak in 2006 (12.8%), the rate of PTB in the US has

gradually declined, reaching 11.6% of all births in 2012 (Martin et al, 2013). For singleton births, the rate of PTB was 11.1% at its peak in 2006, and declined to 9.9% in 2012 (Martin et al, 2013). Overall, rates of prematurity vary by ethnicity and nativity. PTB rates for African Americans are more than twice those for Hispanic or white infants (Alexander et al, 2003), while rates are higher for Hispanics compared to non-Hispanic whites (CDC, 1999; Martin et al, 2010). Among Hispanics, US-born women have a higher risk of delivering preterm infants than their foreign-born counterparts (Flores et al, 2012; Kaufman et al, 2011; Crump et al, 1999). The recent declines in PTB also vary across race and ethnicity, with similar declines in PTB among non-Hispanic black infants and non-Hispanic white infants from 2006 to 2012 (10% and 12% declines, respectively), while Hispanic infants experienced a more modest decline (5%) (Martin et al, 2013).

In the US, preterm birth and related infant health problems were the leading cause of infant death in 2009 (CDC, 2013). Compared with infants born at term, preterm infants have a greater risk of death and disability; approximately 75% of perinatal deaths occur among preterm infants (Slattery & Morrison, 2002), with an inverse relationship between infant mortality rates and gestational age (Mathews & MacDorman, 2013). Preterm infants also have increased prevalence of medical disabilities, learning difficulties, behavioral and psychological problems (Saigal et al, 2003; Aylward et al, 2005; Delobel-Ayoub et al, 2006).

Overall, adverse pregnancy outcomes are 2- to 3-fold more common among infants born to poor urban women (Ventura et al, 1997). Other factors that can affect birth outcomes include inadequate prenatal care, smoking, drinking and substance abuse (NRC, 1990; Kramer, 1987). Additionally, a history of adverse birth outcomes, including spontaneous abortion, preterm

delivery, low birth weight or intrauterine growth restriction in a previous pregnancy, can increase the risk of adverse birth outcomes in the current pregnancy (Kramer, 1987).

1.2.2 Childhood respiratory health

Asthma is a respiratory condition characterized by attacks of difficulty breathing from airway inflammation and bronchial hyperactivity (Eder et al, 2006). In the United States, asthma is a leading cause of chronic childhood illness (Adams et al, 1999) and disability (Newacheck & Halfon, 2000). Compared to the rest of the population, the burden of asthma is greater for children (Mannino et al, 2002) and prevalence among 0-17 year olds has remained relatively constant since the early 2000s (Akinbami et al, 2009). Among 0-4 year olds, the prevalence of asthma, based upon health professional diagnosis, in 2004-2005 was 6.2% and rates were higher in males than females (7.4% and 5.0%, respectively) (Akinbami, 2006). Additionally, there are racial and ethnic disparities in asthma rates: non-Hispanic black children have 1.6 times the prevalence of asthma (12.7%) compared to non-Hispanic whites, while Mexican children have the lowest reports of asthma (6.4%) and Puerto Rican children have the highest (19.2%) among Hispanics (Akinbami, 2006). Apart from genetics, multiple factors are thought to contribute to the risk of asthma, including obesity, exposure to tobacco smoke, environmental and dietary factors (von Mutius & Hartert 2013).

It is important to note that not all types of wheeze in childhood eventually become asthma and several phenotypes of asthma have been described including patterns of 'early transient,' 'persistent' and 'late-onset' wheeze (Martinez et al, 1995). As clinical asthma usually develops between the ages of 5 and 6, wheeze before this age is likely a combination of 'transient' and 'persistent wheeze' (Maslova & Hansen, 2014). For some children, early

wheezing may be related to a predisposition for asthma, especially for children with persistent wheezing (Martinez et al, 1995).

Respiratory infections account for over a third of pediatric consultation to primary care in the United States (Fendrick et al, 2003) and are more common in children less than two years of age (Sidwell & Barnard, 2006). Bronchiolitis, the most prevalent lower respiratory tract infection in young children, is mainly caused by respiratory syncytial virus (RSV) in developed countries (AAP, 2006) and infection with this virus is the leading cause of hospitalization in infants (Shay et al, 1999; Stockman et al, 2012).

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Chapter 2: WIC enrollment and prevention of recurrent preterm birth among eligible California mothers: Analysis of birth certificates from 2007-2011

2.1 Introduction

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is a nationwide program that began in 1972 with the mission of improving the nutritional status and safeguarding the health of low-income pregnant and postpartum women, infants and children under the age of 5 who meet eligibility criteria (WIC, 2014). While it is characterized as a nutrition program, WIC benefits go beyond supplemental food to include counseling, health and social service referrals. Participation has increased in the past decade: nationally, 7.2 million women, infants and children received WIC benefits each month in 2000 compared to 9.2 million in 2010 (WIC, 2014) and 9.7 million in 2012, of whom 10% were pregnant women (Johnson et al, 2013). In California alone, WIC serves over 1.4 million participants each month and 60% of all infants born in California were born to mothers who participated in WIC (CDPH, 2011). Despite widespread enrollment, in 2003 the USDA Food and Nutrition Service found that only 70% of the 1.2 million eligible pregnant women participated in the program nationally (USDA, 2007), while 83% of eligible California women participated between 2007 and 2008 (CDC, 2013).

To be eligible for WIC, pregnant women must meet two requirements. First, they must be income eligible, either because their incomes are at or below 185 percent of the Federal Poverty Level or because they participate in the Temporary Aid to Need Families, Medicaid (Medi-Cal in California), or Food Stamp programs. Second, the pregnant woman must be certified as being at

"nutritional risk," either because she has a medical-based risk (such as a previous poor pregnancy outcome) or because of a diet-based risk (such as an inadequate diet) (WIC, 2014).

The goal of WIC is to decrease the risk of poor birth outcomes and improve the health of its participants during critical times of growth and development, yet previous studies evaluating the program have reported inconsistent findings. Studies of low-income Medicaid enrolled women, meeting the financial criteria for WIC eligibility, suggest that enrollees deliver higher birth weight infants (Kowaleski-Jones & Duncan, 2002) and are less likely to have an adverse birth outcome, such as low birth weight, premature birth or small for gestational age (Bitler & Currie, 2005a; Joyce et al, 2005; Gai & Feng, 2012). Additionally, a study of New York women enrolled in WIC during pregnancy in 1995 reported that early prenatal enrollment resulted in infants that were on average 70 grams heavier at birth than infants of those enrolled late in pregnancy (Lazariu-Bauer et al, 2004). On the other hand, several studies found little or no evidence of WIC influencing birth outcomes (Schramm, 1985; Besharov & Germanis, 1999; Brown et al, 1996; Besharov & Germanis, 2001; Joyce et al, 2008). Additionally, as part of the National WIC Evaluation, neither a historical analysis of WIC participation across counties between 1972 and 1980 nor a smaller, nationally representative longitudinal study of WIC enrollment in the first two trimesters of pregnancy found associations between program participation and birth outcomes (Rush et al, 1988a; Rush et al, 1988b). This lack of consensus in the literature may be due to methodological issues, specifically differences in study design, participant inclusion criteria, time-frame of the study, and location, which may impact the racial/ethnic distribution or neighborhood characteristics of the study population.

Here we examine the possible influence of WIC participation during pregnancy on adverse birth outcomes among California births from 2007 to 2011. One of the goals of WIC is

to improve birth outcomes among eligible women and in this study we assess the impact of WIC enrollment on recurrent preterm birth. Preterm delivery is a risk factor for subsequent preterm birth (Ananth et al, 2006; Mazaki-Tovi et al, 2007) and few, if any, studies have focused on the risk of recurrence by WIC participation. Additionally, having had a previous adverse birth outcome meets the "nutritional risk" criteria for WIC-eligibility, providing means of identifying women eligible for WIC previous studies did not use. We assess whether enrollment in WIC is associated with improved subsequent birth outcomes among Medi-CAL enrolled mothers with a previous preterm birth and distinguish two mutually exclusive subgroups of eligible women: those newly enrolling in the program and those continuing WIC participation.

2.2 Methods

Subject selection

Subjects for the study were selected from state electronic birth records of live births registered in California from 2007, the year systematic WIC enrollment reporting began in California, through 2011. Consecutive singleton siblings born within the four year timeframe were matched to each other to create sibling pairs using LinkPlus software (www.cdc.gov/cancer/registryplus/lp.htm). Linkage was based on the first and last name of mother, mother's Spanish/Hispanic origin, mother's date of birth and birthplace (state or country). Additionally, to ensure identification of consecutive siblings, the date of last live birth on the second-born child's birth certificate was linked to the first-born's date of birth, resulting in a total of 274,648 sibling pairs.

Furthermore, inclusion in the study was based on whether subjects met income and nutritional risk criteria for WIC services as both are required to qualify for benefits (WIC, 2014). Income is not reported on birth records, thus having used Medi-Cal as the primary payer for prenatal care in the second pregnancy served as the proxy measure to identify those meeting the program's financial requirement. Our study population was further limited to those with a previous preterm birth as women with an adverse prior birth outcome meet the "nutritional risk" criteria.

To assess the relationship between WIC participation and risk of recurrent preterm birth, we identified two subgroups of women eligible to receive benefits: first pregnancy WIC non-enrollees (FPN) and first pregnancy enrollees (FPE) (**2.5.1 Table 1**). We identified 2,193 first pregnancy WIC non-enrollees and 8,814 first pregnancy WIC enrollees and we further excluded births (FPN n=228; FPE n=700) with missing or extreme gestational ages (<20 weeks or >45 weeks) and weights (<200g or >5,000g).

Exposure assessment

In the US, state laws require birth certificates to be completed for all births (Kowaleski, 1997). Standardized forms for the collection of birth data include two worksheets: mother and facility. Information collected on the mother's worksheet include: residence, nativity, race/ethnicity, age, educational attainment of both parents, in addition to anthropometric measures and cigarette smoking behavior of the mother. The facility worksheet collects medically pertinent data obtained from medical records such as conditions and complications during pregnancy, birth weight, and method of delivery. In 2007, birth certificates began including information on WIC enrollment. Mother's enrollment in WIC was assessed from the

following question on the mother's worksheet: "Did you receive WIC (Women, Infants & Children) food for yourself because you were pregnant with this child?"

Outcome assessment

Gestational age was calculated based on the interval from date of last menstrual period (LMP) to birth. To assess prematurity, preterm birth (PTB), defined as birth prior to the completion of 37 weeks or 259 days gestation, was dichotomized with term births serving as the reference.

Covariate assessment

Information on demographics and health behaviors during pregnancy were obtained from California State electronic birth certificates. Covariates used in analyses include mother's race/ethnicity (non-Hispanic white, Hispanic white, Black, Asian/Other) and nativity (US born, foreign born), mother's age at pregnancy (<24, 25-29, 30+), mother's education at the time of pregnancy (≤11 years, 12 years, ≥13 years), first pregnancy payer of prenatal care as a proxy for income history (Medi-Cal, private insurance, other), interpregnancy interval (<18 months, ≥18 months; definition of an "ideal" minimum interpregnancy interval according to Conde-Agudelo et al, 2006), initiation of prenatal care for index pregnancy (first trimester, after first trimester/never), cigarette use before and after conception, pre-pregnancy BMI (<24.9 kg/m^2, ≥25.0 kg/m^2), weight gain during pregnancy (based on Institute of Medicine 2009 recommendations (IOM, 2009): less than recommended, met recommendation, more than recommended), and child's gender (male, female).

Statistical analyses

We used log binomial regression to estimate risk ratios (RRs) for WIC enrollment and recurrent preterm birth for the two subgroups of eligible women, separately. For both groups (FPN and FPE), we assessed whether staying off or dropping WIC in the second pregnancy was associated with adverse birth outcomes, respectively. Among first pregnancy WIC non-enrollees, women who newly picked up WIC in the second pregnancy served as the referent group while among first pregnancy WIC enrollees, women who maintained WIC enrollment in their second pregnancy served as the referent group. We also assessed the possible effects of WIC enrolment on gestational age as a continuous variable (in weeks) in multiple linear regression analyses.

Multivariate analyses included the following potential confounders on the basis of previous literature (Goldenberg et al, 2008): maternal race/ethnicity, education, age, pre-pregnancy BMI, and cigarette consumption during pregnancy. To address possible residual confounding by socioeconomic status, a proxy for income history (first pregnancy primary payer of prenatal care) was also included in adjusted analyses. Additionally, as the rate of preterm birth in California declined from 11.1% in 2007 to 9.8% in 2011 (CDPH, 2015) and the WIC food package was revised in 2009 (USDA, 2009), we also included an indicator for birth year in analyses (a categorical variable with five categories, one for each year). Few women indicated medical disorders including diabetes (FPN, n=90; FPE, n=266), hypertension (FPN, n=68; FPE, n=219), and eclampsia (FPN, n=3, FPE, n=8), but in sensitivity analyses we excluded these women to assess their impact on the associations. Furthermore, to assess heterogeneity within subgroups, we performed stratified analyses by first birth primary payer of prenatal care (Medi-

Cal, no Medi-Cal), maternal race/ethnicity, nativity, age, education and interpregnancy interval where sample size permitted.

Data were analyzed using the SAS statistical software package version 9.3 (SAS Institute, Inc. Cary, North Carolina).

2.3 Results

The overall number of live births and total singleton births in California dropped by 11.3% and 11.4%, respectively, between 2007 and 2011. Over this time, participation in WIC increased by 7.8% while participation in Medi-Cal increased 2.6% from 2007 to 2010 (**2.5.2 Figure 1**).

First pregnancy WIC non-enrollees: FPN mothers who did not participate in WIC in their second pregnancy were older, more educated, White, with a lower BMI (kg/m^2) compared with enrollees (**2.5.3 Table 2**). Among these eligible women who did not enroll in WIC in their first pregnancy, second pregnancy non-enrollees had an increased risk of recurrent preterm birth (RR_{adj} 1.42, 95%CI (1.15, 1.76) compared to enrollees (**2.5.4 Table 3**) and as expected non-enrollees delivered infants at a younger gestational age (weeks, β_{adj} -0.31, 95%CI (-0.58, -0.04)) than children of new WIC enrollees.

First pregnancy WIC enrollees: FPE women who dropped WIC in the second pregnancy were more educated, later initiators of prenatal care, US-born White, with a lower BMI (kg/m^2) compared with those continuing to be served by WIC (**2.5.3 Table 2**). Among these eligible women previously enrolled in WIC, second pregnancy non-enrollees had a small increase in risk for experiencing a recurrent preterm birth (RR_{adj} 1.15, 95%CI (0.97, 1.36) compared to enrollees

(**2.5.4 Table 3**) and as expected non-enrollees delivered infants at a younger gestational age (weeks, β_{adj} -0.34, 95%CI (-0.58, -0.10)) compared to enrollees.

Sensitivity analyses: Excluding births to mothers who had a history of diabetes, hypertension or eclampsia did not impact results (*data not shown).* Stratified analyses revealed heterogeneity in point estimates according to mother's first pregnancy primary payer for prenatal care (**2.5.5 Figure 2**). Within subgroups, for first pregnancy Medi-Cal enrollees (FPN/Medi-Cal and FPE/Medi-Cal) the association between WIC participation and recurrent preterm birth was stronger compared to that of non-Medi-Cal enrolled women (FPN/Non Medi-Cal and FPE/Non Medi-Cal, respectively). Among FPN the association between program participation and birth outcome was strongest for Black mothers, followed by Hispanics, while no association was observed among White mothers (**2.5.6 Figure 3**). The strength of the association was also influenced by maternal age and interpregnancy interval for FPN births: young maternal age (**2.5.7 Figure 4**) and shorter time between births (**2.5.8 Figure 5**) in WIC non-enrollees increased the risk of recurrent preterm birth. No such heterogeneity in effect estimates was observed in FPE births and we did not find any influence on the association between program participation and birth outcome by mother's nativity or education in either group (*data not shown*).

2.4 Discussion

In the present study, we set out to assess whether WIC enrollment during pregnancy was associated with birth outcomes among eligible women. Among those born between 2007 and 2011, selecting siblings from California birth records allowed for the identification of a

representative sample of parous women who would qualify for WIC services in the second of two pregnancies according to both financial, use of Medi-CAL as the second pregnancy primary payer of prenatal care, and "nutritional risk" criteria, previous premature birth. We further divided eligible women into two mutually exclusive groups: first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE). For FPN, we assessed whether staying off WIC in the second pregnancy increased the risk of adverse birth outcomes compared to women who newly enroll in the program, while among FPE we assessed whether dropping WIC in the second pregnancy increased the risk for adverse birth outcomes compared those who continue their enrollment in the program. In our analyses, we found that regardless of being FPN or FPE, eligible women with a previous preterm birth who did not enroll in WIC in the second pregnancy had an increased risk of recurrent premature birth and delivered babies earlier (gestational age in weeks) compared to enrollees.

While we found that enrolling in WIC during pregnancy improved birth outcomes among WIC eligible women, we do not know which aspects of the program may be responsible. The WIC program provides three main benefits to eligible participants, including the provision of vouchers for food supplementation, counseling, and referrals to health care and social services (El-Bastawissi et al, 2007). WIC may promote healthy birth outcomes through the provision of vouchers for nutritious foods that aid in fetal development, such as foods high in protein, iron, calcium, vitamin A, and vitamin C (WIC, 2014). The program may also impart benefits to the developing fetus through counseling and education classes or referrals to health and other social agencies, which may encourage beneficial maternal behaviors (Bitler & Currie 2005; Joyce et al, 2005). Additionally, to continue to receive the WIC benefits, women enrolled in the program are

followed up throughout pregnancy during recertification appointments, which may also help women opt for and sustain healthier behaviors throughout pregnancy (Bitler & Currie, 2005b).

Previous research does not distinguish between first-time enrollees nor recurrent adverse birth outcome, yet the association we observed between WIC participation and preterm birth among WIC eligible women is consistent with previous findings. In a multi-state analysis of Medicaid enrolled pregnant women across 19 states that met WIC's income criteria between 1992 and 1999, prenatal enrollment in WIC resulted in an approximate 30% decreased risk of premature birth outcomes compared to non-enrollees (Bitler & Currie, 2005a). It should be noted that a criticism of previous WIC studies is a failure to address the possibility of selection bias; not all WIC eligible women choose to participate thus enrollees may have been different from non-enrollees (Besharov & Germanis, 2001). For instance, it has been suggested that women who participate in the program may have stronger social or support networks, potentially increasing awareness of the program, and that participants may be those most interested in the health of their children (Gai & Feng, 2012; Lee & Mackey-Bilaver, 2007; Kowaleski-Jones & Duncan, 2002). As such, participants are not only more motivated to enroll in the program but are also more likely to give birth to healthy children compared to non-participants and previous studies that did not account for such self-selection into the program may have overestimated the benefits WIC provides. Our findings are also consistent with a more recent study of a nationally representative sample of 14,000 children born in the year 2001 that found WIC participation was associated with a lower probability of very premature birth outcomes compared to non-enrollees after accounting for possible selection bias through instrumental variable analysis (Gai & Feng, 2012).

In our study, we also identified possible effect measure modifiers (EMM) of the association between WIC participation and birth outcomes. In stratified analyses, we found heterogeneity in the association by first pregnancy payer of prenatal care, race/ethnicity, age, and birth spacing: the association between WIC enrollment and recurrent preterm birth was strongest for women who were served by Medi-Cal in the first pregnancy, Black and Hispanic mothers, those <24 years of age, and mothers having their second child within 18 months of their first birth. Therefore, while current efforts targeting eligible low-income, underserved pregnant women should continue, we have identified high-risk subgroups of the population to whom additional WIC enrollment efforts may be directed for the prevention of recurrent adverse birth outcomes. As in previous studies, while these findings may also be subject to selection bias, our analysis of FPE mothers mitigates this concern. These women represent an interesting, previously unstudied group and analyses of this eligible subgroup are less likely influenced by selection bias: all women received WIC benefits during their first pregnancy and therefore share unmeasured factors such as motivation for enrollment or interest in child's well-being that drove them to participate during their first pregnancy. While associations are attenuated in the FPE subgroup compared to FPN, our finding of an association between WIC non-enrollment and increased risk of recurrent preterm birth is robust.

To date, there has not been an evaluation of the WIC program since systematic collection of WIC enrollment on California birth certificates commenced, providing a unique opportunity to evaluate the program in a universal, population-based manner. As much of the previous literature focuses on data from the 1990's to the early 2000's, this information may be out of date considering the proportion of Medicaid births increased 19% nationwide between 2008 and 2010 (Markus et al, 2013). A strength of this study is the large and rich dataset, allowing for analysis

of population subgroups that are often understudied. Those who are eligible for WIC represent a heterogeneous group of women and we identified two mutually exclusive subgroups according to history of WIC enrollment. Due to the large sample size, we also performed stratified analyses of the association between program participation and adverse birth outcomes to identify vulnerable subgroups among eligible women. Moreover, the identification of consecutive pregnancies allowed for the assessment of recurrent preterm birth among a representative sample of parous women, which is a novel contribution to the literature.

This study is limited as WIC participation is self-reported by the mother on the birth certificate (dichotomous yes or no for receipt of services for the pregnancy), thus, we are unable to determine the timing or duration of prenatal WIC enrollment (early versus late in pregnancy). Additionally, the WIC income criterion is assessed through Medi-CAL as the second pregnancy primary payer of prenatal care, yet healthcare coverage can change during pregnancy, affecting the ability to accurately determine eligibility for WIC. Also, as the source of information for this study was birth certificates, it consists of a survivor population and includes only those conceptions that survive to be born alive.

In this representative sample of California parous mothers, while WIC enrollment improves birth outcomes among eligible women overall, the magnitude of the association varies according to various maternal characteristics. Among first pregnancy WIC non-enrollees, low-income, younger, Black and Hispanic second pregnancy WIC non-enrollees with the shortest intervals between pregnancies have the highest risk for recurrent adverse birth outcomes. The identification of high risk subgroups of eligible non-enrollees calls for future research that assesses reasons for non-enrollment in the WIC program by these women. As WIC participation

is a modifiable behavior, such additional information may better inform targeted interventions to increase program enrollment among eligible women at high risk of an adverse birth outcome.

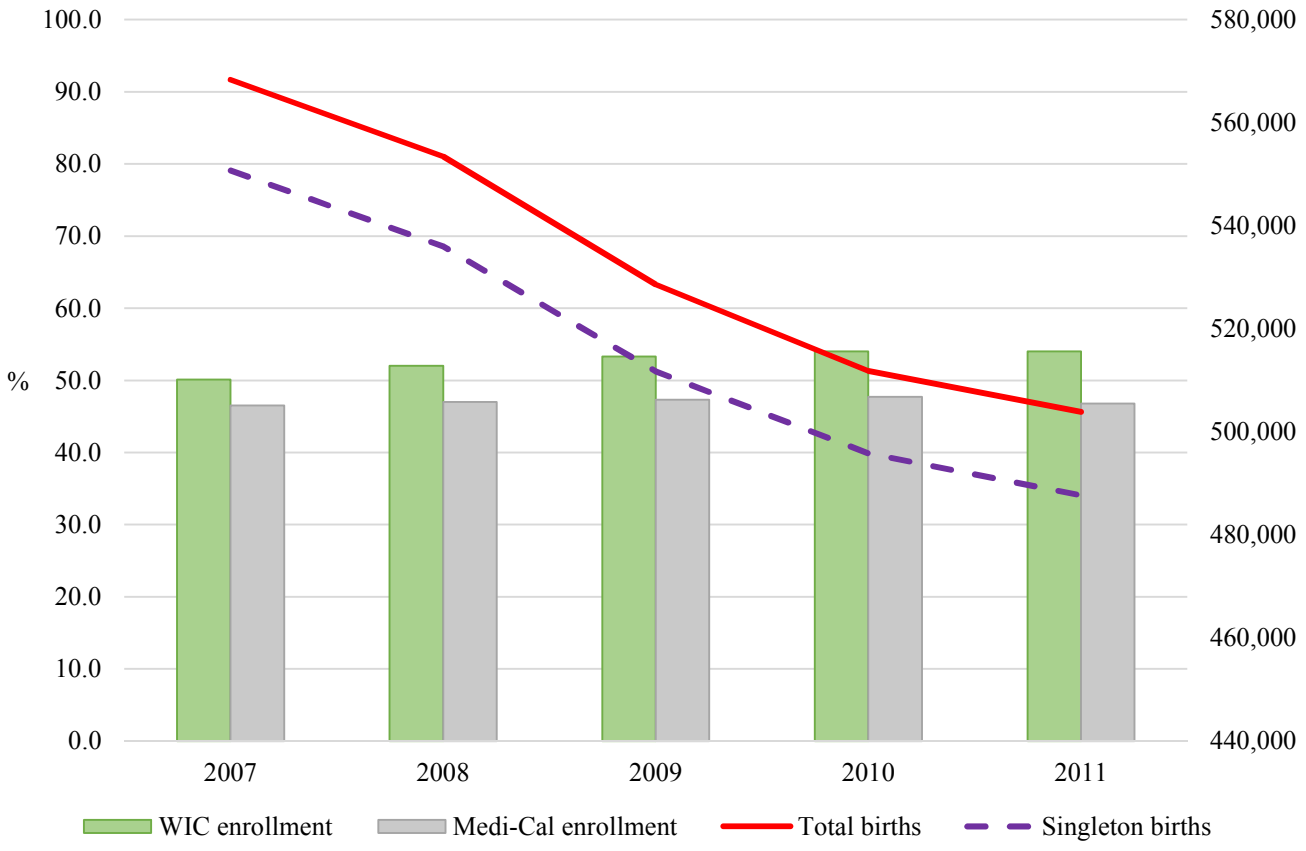
2.5 Tables and Figures

2.5.1 Table 1. Descriptive characteristics of singleton California births from 2007-2011 and siblings included in analyses for study objectives.

	FPN[a] (n=1,965)		FPE[b] (n=8,114)	
	First pregnancy	Second pregnancy	First pregnancy	Second pregnancy
Primary payer of prenatal care	n (%)	n (%)	n (%)	n (%)
Medi-Cal	1,085 (55)	1,965 (100)	7,025 (87)	8,114 (100)
Private insurance	673 (34)	-	707 (9)	-
Other	136 (7)	-	344 (4)	-
No prenatal care	71 (4)	-	38 (0)	-
WIC participation during pregnancy				
Yes	-	1,418 (72)	8,114 (100)	7,460 (92)
No	1,965 (100)	547 (28)	-	654 (8)
Birth year				
2007	943 (48)	6 (0)	3,526 (43)	10 (0)
2008	599 (30)	169 (9)	2,546 (31)	652 (8)
2009	309 (16)	439 (22)	1,515 (19)	1,681 (21)
2010	113 (6)	630 (32)	520 (6)	2,583 (32)
2011	1 (0)	721 (37)	7 (0)	3,188 (39)
Birth outcome				
Term birth	-	1,597 (81)	-	6,586 (81)
Preterm birth	1,965 (100)	368 (19)	8,114 (100)	1,528 (19)

[a] First pregnancy WIC non-enrollees (FPN).
[b] First pregnancy WIC enrollees (FPE).

2.5.2 Figure 1. Women, Infants and Children (WIC) and Medi-Cal enrollment by year in California birth records.



2.5.3 Table 2. Descriptive characteristics of California sibling births from 2007 to 2011 by study subgroup and second pregnancy WIC participation.

	FPN[a]			FPE[b]		
	All (n=1,965)	No WIC (n=547)	New WIC enrollee (n=1,418)	All (n=8,114)	Drop WIC (n=654)	Maintain WIC (n=7,460)
	Mean±SD or n(%)			Mean±SD or n(%)		
Demographic and behavioral characteristics						
Race/ethnicity						
Non-Hispanic white	503 (26)	197 (36)	306 (22)	783 (10)	129 (20)	654 (9)
Hispanic	951 (49)	195 (36)	756 (53)	5,992 (74)	375 (57)	5,617 (75)
Black	195 (10)	62 (11)	133 (9)	646 (8)	92 (14)	554 (7)
Asian	226 (12)	77 (14)	149 (11)	415 (5)	34 (5)	381 (5)
Other	85 (4)	14 (3)	71 (5)	267 (3)	24 (4)	243 (3)
Nativity						
US born	1,345 (69)	390 (71)	955 (67)	4,382 (54)	461 (70)	3,921 (53)
Foreign born	620 (31)	157 (29)	463 (33)	3,732 (46)	193 (30)	3,539 (47)
Mother's age						
≤24 years	1,043 (53)	253 (46)	790 (56)	5,375 (66)	443 (68)	4,932 (66)
25-29 years	517 (26)	141 (26)	376 (27)	1,737 (21)	149 (23)	1,588 (21)
≥30 years	405 (21)	153 (28)	252 (18)	1,002 (12)	62 (9)	940 (13)
Mother's education						
<12 years	516 (27)	94 (18)	422 (31)	3,298 (42)	188 (30)	3,110 (43)
12 years	661 (35)	186 (35)	475 (35)	2,917 (37)	262 (42)	2,655 (36)
≥13 years	721 (38)	250 (47)	471 (34)	1,703 (22)	175 (28)	1,528 (21)
Income history: First pregnancy primary payer for prenatal care						
Medi-Cal	1,085 (55)	291 (53)	794 (56)	7,025 (87)	529 (81)	6,496 (87)
Private insurance	673 (34)	209 (38)	464 (33)	707 (9)	86 (13)	621 (8)
Other	207 (12)	47 (9)	160 (11)	382 (5)	39 (6)	343 (5)
Interpregnancy interval						
<18 months	509 (26)	131 (24)	378 (27)	2,203 (27)	164 (25)	2,039 (27)
≥18 months	1,456 (74)	416 (76)	1,040 (73)	5,911 (73)	490 (75)	5,421 (73)
Prenatal care initiation						
Trimester 1	1,362 (71)	368 (69)	994 (71)	6,062 (76)	433 (68)	5,629 (76)
Trimester 2, 3 or never	569 (29)	164 (31)	405 (29)	1,948 (24)	206 (32)	1,742 (24)
Cigarette use before conception[c]						
Yes	128 (7)	44 (8)	84 (6)	263 (3)	40 (6)	223 (3)
No	1,816 (93)	500 (92)	1,316 (94)	7,737 (97)	613 (94)	7,124 (97)
Cigarette use during pregnancy						
Yes	105 (5)	36 (7)	69 (5)	212 (3)	34 (5)	178 (2)
No	1,842 (95)	509 (93)	1,333 (95)	7,788 (97)	619 (95)	7,169 (98)
Pre-pregnancy BMI (kg/m^2)						
<24.9 kg/m2	862 (49)	255 (52)	607 (47)	3,384 (47)	298 (52)	3,086 (46)
≥25.0kg/m2	909 (51)	234 (48)	675 (53)	3,832 (53)	270 (48)	3,562 (54)
Weight gain during pregnancy[d]						
Less than recommendation	493 (28)	131 (27)	362 (28)	2,168 (30)	181 (32)	1,987 (30)
Met recommendation	581 (33)	178 (36)	403 (31)	2,366 (33)	172 (30)	2,194 (33)
More than recommendation	697 (39)	180 (37)	517 (40)	2,682 (37)	215 (38)	2,467 (37)

Child's gender						
Male	1,008 (51)	291 (53)	717 (51)	4,144 (51)	348 (53)	3,796 (51)
Female	957 (49)	256 (47)	701 (49)	3,970 (49)	306 (47)	3,664 (49)
Maternal medical conditions						
Pre-pregnancy diabetes	15 (1)	5 (1)	10 (1)	47 (1)	2 (0)	45 (1)
Gestational diabetes	75 (4)	26 (5)	49 (4)	219 (3)	18 (3)	201 (3)
Pre-pregnancy hypertension	12 (1)	5 (1)	7 (0)	30 (0)	3 (0)	27 (0)
Gestational hypertension	56 (3)	22 (4)	34 (2)	189 (2)	20 (3)	169 (2)
Eclampsia	3 (0)	1 (0)	2 (0)	8 (0)	1 (0)	7 (0)
Second birth outcomes						
Birth weight (grams)	3,165±580	3,125±633	3,180±558	3,163±583	3,089±657	3,170±576
Gestational age (weeks)	38±3	38±3	38±2	38±3	38±3	38±3
Birth outcomes						
Term birth	1,597 (81)	420 (77)	1,177 (83)	6,586 (81)	507 (78)	6,079 (81)
Preterm birth	368 (19)	127 (23)	241 (17)	1,528 (19)	147 (22)	1,381 (19)

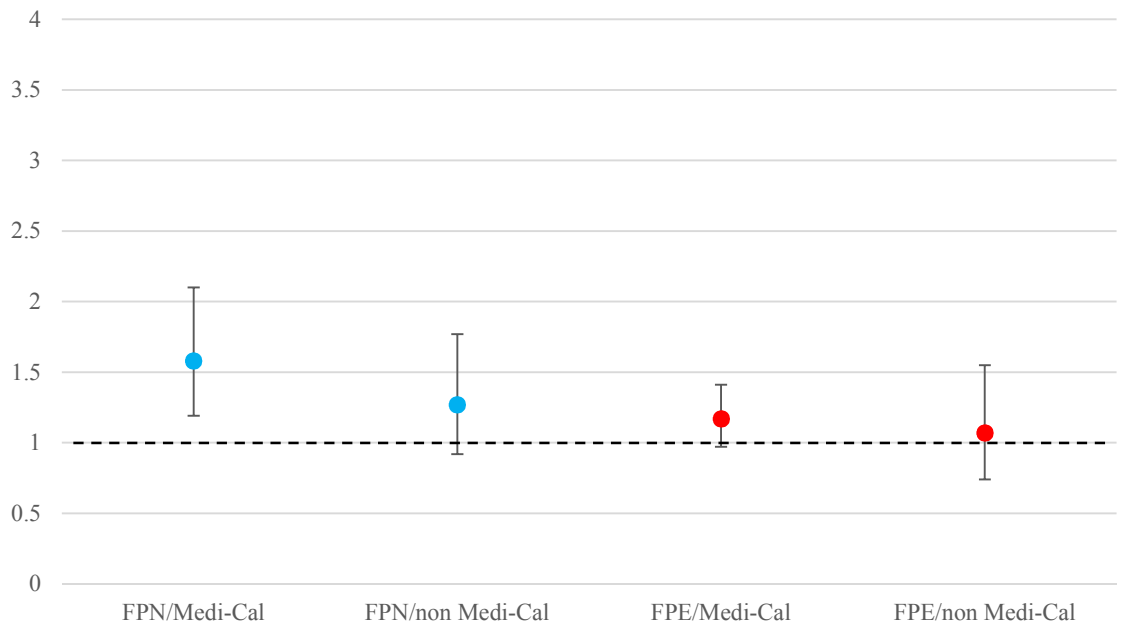
[a] First pregnancy WIC non-enrollee (FPN).
[b] First pregnancy WIC enrollee (FPE).
[c] Cigarette use before conception: 3 months before pregnancy
[d] Weight gain categories are based on BMI from 2009 Institute of Medicine recommendations (IOM, 2009)

2.5.4 Table 3. Regression analysis of WIC participation[a] in second pregnancy and birth outcomes by subgroup[b] among eligible California births from 2007 to 2011.

	Preterm Birth		Gestational age (weeks)	
	RR_{Crude} (95% CI)	RR_{Adj} (95% CI)[c]	β_{Crude} (95% CI)	β_{Adj} (95% CI)[c]
FPN (n=1,965)	1.37 (1.13, 1.65)	1.42 (1.15, 1.76)	-0.29 (-0.55, -0.04)	-0.31 (-0.58, -0.04)
FPE (n=8,114)	1.21 (1.05, 1.41)	1.15 (0.97, 1.36)	-0.38 (-0.60, -0.16)	-0.34 (-0.58, -0.10)

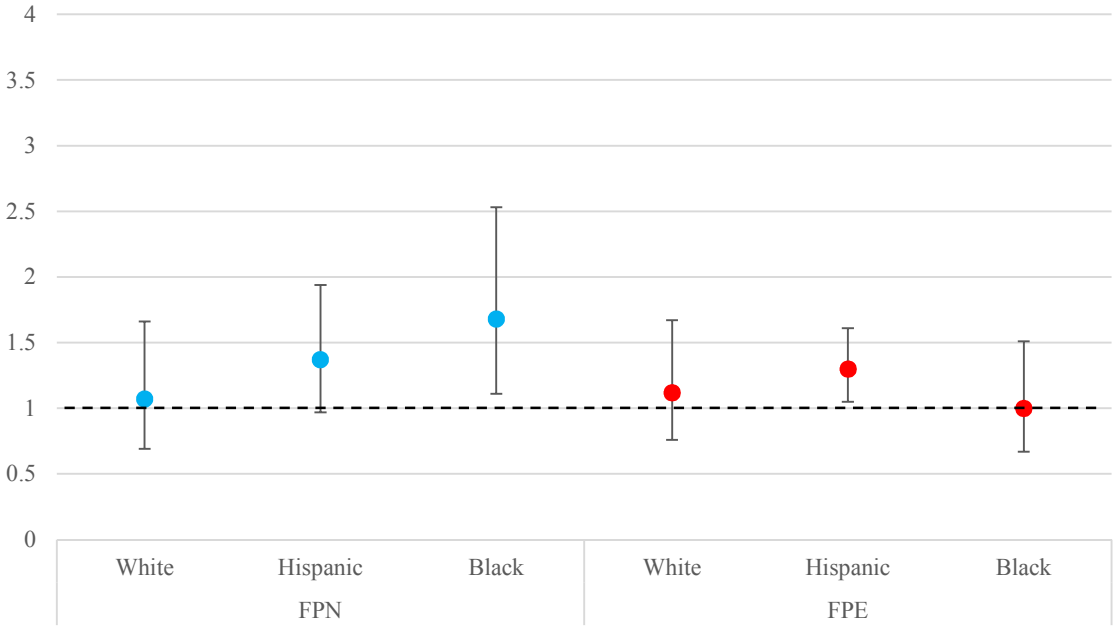
[a] WIC enrollees constitute the reference group: among first pregnancy WIC non-enrollees (FPN) we assess whether continuing to stay off WIC in the second pregnancy increases the risk of preterm birth compared to new enrollees, while among first pregnancy WIC enrollees (FPE) we assess whether dropping WIC in the second pregnancy increases the risk for preterm birth compared to those who maintain program enrollment.
[b] Subgroups are mutually exclusive and include first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE).
[c] Models adjusted for mother's race/ethnicity, age, education, income history (first pregnancy payer of prenatal care), pre-pregnancy BMI (kg/m^2), cigarette use during pregnancy and child's birth year.

2.5.5 Figure 2. Adjusted risk ratios[a] for WIC participation in second pregnancy and birth outcome by subgroup[b] and income history[c] among California birth records from 2007 to 2011.



[a] Models adjusted for mother's race/ethnicity, age, education, pre-pregnancy BMI (kg/m^2), cigarette use during pregnancy and child's birth year.
[b] Subgroups are mutually exclusive and include first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE).
[c] Income history defined as a binary variable for first pregnancy primary payer of prenatal care: Medi-Cal enrollees or non Medi-Cal enrollees.

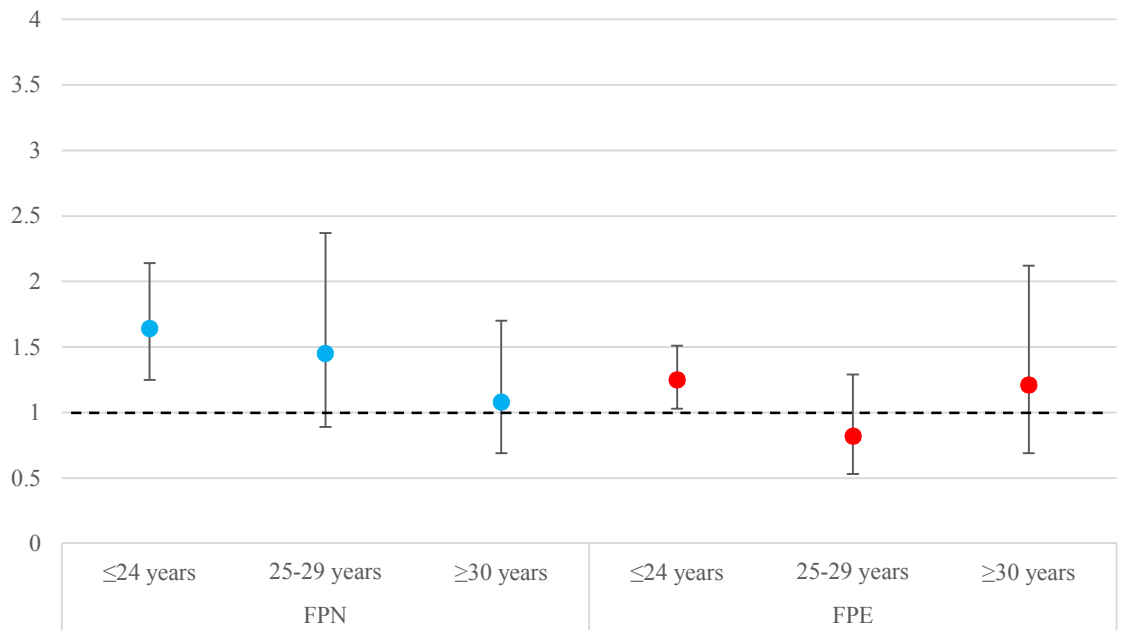
2.5.6 Figure 3. Adjusted risk ratios[a] for WIC participation in second pregnancy and birth outcome by subgroup[b] and race/ethnicity among California birth records from 2007 to 2011.



[a] Models adjusted for mother's age, education, income history (first pregnancy payer of prenatal care), pre-pregnancy BMI (kg/m^2), cigarette use during pregnancy and child's birth year.

[b] Subgroups are mutually exclusive and include first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE).

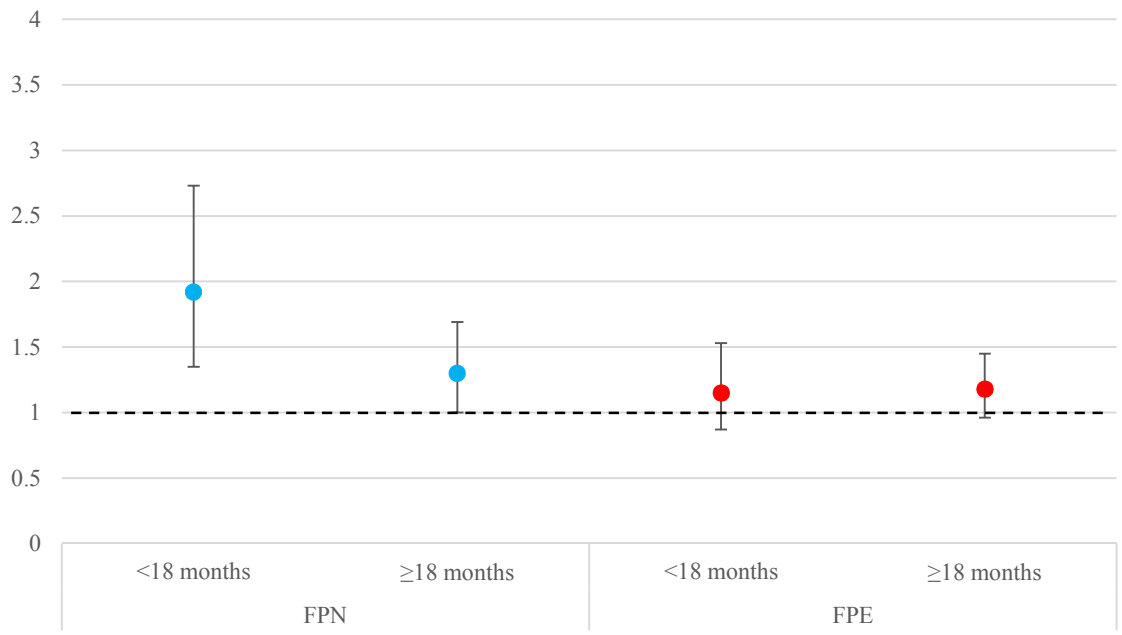
2.5.7 Figure 4. Adjusted risk ratios[a] for WIC participation in second pregnancy and birth outcome by subgroup[b] and mother's age among California birth records from 2007 to 2011.



[a] Models adjusted for mother's race/ethnicity, education, income history (first pregnancy payer of prenatal care), pre-pregnancy BMI (kg/m^2), cigarette use during pregnancy and child's birth year.

[b] Subgroups are mutually exclusive and include first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE).

2.5.8 Figure 5. Adjusted risk ratios[a] for WIC participation in second pregnancy and birth outcome by subgroup[b] and interpregnancy interval among California birth records from 2007 to 2011.



[a] Models adjusted for mother's race/ethnicity, education, income history (first pregnancy payer of prenatal care), pre-pregnancy BMI (kg/m^2), cigarette use during pregnancy and child's birth year.

[b] Subgroups are mutually exclusive and include first pregnancy WIC non-enrollees (FPN) and first pregnancy WIC enrollees (FPE).

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Chapter 3: The influence of pre-natal supplement initiation on preterm birth among Hispanic women in Los Angeles County: the role of nativity

3.1 Introduction

Infant health problems related to preterm birth (PTB, <37 completed weeks gestation) are the leading cause of infant death in the United States (CDC, 2013). While gestational age at birth among preterm births influences the severity of adverse outcomes, prematurity in general is a risk factor for subsequent morbidity, mortality, and long-term health issues (Delobel-Ayoub et al, 2006; Aylward et al, 2005; Hack et al, 2005; Marlow et al, 2005; Saigal et al, 2003; Bhutta et al, 2002).

Since 1981, there has been a 30% increase in the preterm birth rate in the US (Davidoff et al, 2006) and despite efforts, the rate of prematurity increased from 11.6% in 2000 to 12.7% in 2007 (NCHS, 2012). Rates of preterm birth are higher for Hispanics compared to non-Hispanic whites (CDC, 1999; Martin et al, 2010) and US-born Hispanic women are at higher risk of delivering preterm infants than their foreign-born counterparts (Flores et al, 2012; Kaufman et al, 2011; Crump et al, 1999; Singh & Yu, 1996).

Previous research suggests that a woman's nutritional status and supplement use both before and during pregnancy are important for optimal pregnancy outcomes. Compared with nonusers, women who use multivitamin supplements prior to conception have a reduced risk of preterm birth (Vahratian et al, 2003). Additionally, periconception multi-vitamin use lowered the odds of very preterm (<34 weeks) but not moderate preterm (34-<37 weeks) birth (Catov et al, 2007). A follow-up study found that this relationship was present only among women with

pregravid BMI less than 25kg/m^2 (Catov et al, 2011). Moreover, women with nutrient deficiencies (Ronnenberg et al, 2002; Zhou et al, 1998) or low intakes of vitamins and minerals, including folate, in early to mid-pregnancy were found to have higher rates of preterm birth (Siega-Riz et al, 2004; Siega-Riz et al, 2003; Scholl et al, 1997; Shaw et al, 1997). A more recent study of Hungarian primiparous pregnant women found that any reported folic acid use throughout pregnancy decreased odds of PTB outcome while use in all three trimesters resulted in even lower odds of PTB compared to non-users (Czeizel et al, 2010). Despite such results in observational studies, randomized control trials of multivitamin supplement use in pregnancy failed to support these findings (Czeizel et al, 1994). Such discordance may be due to methodological issues, different supplements under study or assessment techniques for vitamin intake, preterm birth classification, incomplete or lack of control for confounding factors, rates of attrition or heterogeneity of study populations under consideration, including baseline nutritional status.

While few studies have been conducted on US pregnant women, the National Health and Nutrition Examination Survey revealed that dietary supplement use in the population varies by ethnicity (Bailey et al, 2011; Gahche et al, 2011), with Hispanic adults less likely to take vitamin and mineral supplements compared to blacks and non-Hispanic whites (Shelton et al, 2009). Given that dietary status affects pregnancy outcomes and US-born Hispanic women may adopt a diet lacking in micro-nutrients essential for pregnancy compared to their foreign-born counterparts (Harley et al, 2005; Guendelman & Abrams, 1995), it is of interest to investigate the use of supplements during preconception and prenatal periods in order to better target prevention and health educational efforts. The aim of this study is to examine associations between the timing of pre-natal supplement initiation in pregnancy and preterm birth in a sample of Hispanic,

majority immigrant, and non-Hispanic white women in the Environment and Pregnancy Outcomes Study (EPOS), a case-control study nested within the 2003 cohort of over 53,000 births in Los Angeles County.

3.2 Methods

Sample and Data Collection

The UCLA Environment and Pregnancy Outcomes Study (EPOS) is a case-control study nested within the year 2003 birth cohort of all women who resided in more than one third of Los Angeles (LA) County. The details of subject selection are described elsewhere (Ritz et al, 2007). Briefly, the original goals were to study the effects of ambient air pollution on adverse birth outcomes. California state and LA County electronic birth certificate records were used to select live singleton births to mothers residing near air pollution monitoring stations and/or major roadways. All cases of preterm birth (<37 weeks gestation) and low birthweight (<2,500 grams) were included from 24 zip codes near air monitoring stations, and a random sample of 30% of cases from the remainder of the 87 zip code areas. Controls (full-term newborns, weighing ≥2,500 grams) were matched to cases based on birth month and zip code set for a total sample of 6,374 women. With a response rate of 40%, a total of 2,543 women were enrolled 3-6 months postpartum. Mothers were interviewed in English or Spanish by telephone, mail survey, or home visit. This work was approved by the UCLA Office for the Protection of Human Subjects and the California Committee for the Protection of Human Subjects.

For the analyses presented in this paper, only non-Hispanic white (NHW) and Hispanic white women were included in the final study population (n=2,123), representing 84% of the

respondent population. NHW and Hispanics were the largest race/ethnicity groups (17% and 67%, respectively) among EPOS survey respondents.

Information about maternal age, race/ethnicity, education, nativity, parity, and prenatal care was obtained from California State and Los Angeles County electronic birth certificate records. The EPOS survey questionnaire elicited detailed information on health behaviors and risk factors such as smoking, alcohol consumption, and supplement use.

Vitamin use

The EPOS survey instrument elicited information on timing and frequency of various vitamins used in both preconception and prenatal periods. Preconception vitamin use was assessed by asking: "Just before you got pregnant, were you taking multivitamins, pre-natal vitamins, or folic acid?" The frequency was indicated as: "yes-every day or almost every day", "yes-sometimes", and "no". Individuals who indicated any use in preconception were identified as preconception vitamin users. Prenatal vitamin use was assessed by asking: "Did you take any of the following vitamin supplements while you were pregnant: pre-natal vitamins, multivitamins, vitamin C, iron and 'other' supplements." Respondents were asked to indicate use (yes/no) of the individual supplements during each trimester. Additionally, respondents were asked to indicate the frequency of vitamin use during the trimesters in which they indicated use, with the following response categories: "once a month," "once a week," "about 3 days a week," and "every day." Data on dose or brand of supplement were not collected.

The possible combinations of the vitamin use variables are provided in **3.5.1 Table 1**. Vitamin use categories were based upon initiation of use using three mutually exclusive groups: (1) preconception initiation; (2) first trimester initiation; (3) late prenatal (second or third

trimester) initiation or no use. Individuals that failed to provide information on pre-natal supplements yet supplied information for other vitamins during the prenatal period (termed informed missing) were categorized as non-users, while subjects with responses missing for all vitamin supplements during the prenatal period were left as missing. Informed missing subjects (n=42) were included in primary analyses and to assess the influence of these individuals on results, analyses were repeated without these subjects.

Statistical methods

We used logistic regression to estimate odds ratios (ORs) for each pre-natal vitamin initiation time period (preconception, first trimester, and late prenatal/never) and preterm birth (<37 weeks gestation). The following individual-level variables were assessed as potential confounders: maternal race/ethnicity (Non-Hispanic White, Hispanic); maternal nativity (US-born, foreign-born); maternal age (<20, 20-24, 25-29, 30-34, 35+ years); maternal education (≤8, 9-11, 12, 13-15, 16+ years); start of prenatal care (first trimester, after first trimester/never); pre-pregnancy BMI (<18.5kg/m^2, 18.5-24.9kg/m^2, 25.0-29.9kg/m^2, ≥30kg/m^2); alcohol use during pregnancy (yes, no); exposure to environmental tobacco smoke in the home (yes, no); having a previous preterm birth (yes, no); marital status (married or cohabitating, single/divorced/separated); socioeconomic status assessed through the proxy measure of payment for prenatal care (private insurance, other insurance/no insurance). As 31% of foreign born Hispanic mothers with information on pre-pregnancy weight had missing values for height, the median value of height of foreign-born Hispanic mothers (63 inches) was imputed for these women for the calculation of BMI. Multivariate analyses included those potential confounding factors that changed the crude point estimate by approximately 10% or more.

Subgroup analyses were conducted according to mother's race/ethnicity to assess potential effect measure modification of the relationship between pre-natal vitamin use and PTB. Among Hispanics, respondents were further stratified by nativity (US- or foreign-born). Odds ratios (ORs) for preterm birth were calculated with term, normal weight infants (TNW), defined as infants born >37 weeks gestation and weighing ≥2,500 grams, as the reference group. Data were analyzed using the SAS statistical software package version 9.3 (SAS Institute, Inc. Cary, North Carolina).

3.3 Results

Among vitamin users, the majority of respondents reported continued use of pre-natal vitamins throughout pregnancy once they had initiated use (**3.5.1 Table 1**). Preconception pre-natal vitamin initiators were older and more educated, more likely to have experienced a previous adverse birth event and more likely to be of a higher socioeconomic status compared to later initiators (**3.5.2 Table 2**). Non-Hispanic white mothers reported preconception initiation more frequently while Hispanic mothers, regardless of nativity, most frequently reported initiation during the prenatal period. Mothers who gave birth to a term, normal weight infant had higher reports of preconception initiation compared to mothers with a PTB infant.

Among Hispanic respondents, the majority were foreign born and of Mexican, Mexican-American or Chicano descent (**3.5.3 Table 3**). Although those born in the US were younger and less likely to be married or cohabitating, they were more educated and more likely to be of higher socioeconomic status compared to foreign-borns. US-born women had a higher

prevalence of pregravid obesity and higher exposure to both home environmental tobacco smoke and alcohol use during pregnancy compared to their foreign-born counterparts.

Pre-natal vitamin use initiation was associated with preterm birth among Hispanic mothers and the estimated effect differed by nativity (**3.5.4 Table 4**). Among US-born Hispanic women, those reporting initiation during the prenatal period had increased odds of preterm birth compared to those initiating prior to conception. Odds ratios for preterm birth also increased for foreign-born Hispanic women the later a woman initiated pre-natal supplement use, yet the relationship was slightly attenuated compared to US-born women. Findings did not change with the removal of informed missings (*data not shown*).

3.4 Discussion

We conducted a population based case-control study of preterm birth with majority immigrant Hispanic women. Non-Hispanic white mothers were more likely to report preconception initiation of pre-natal supplements whereas Hispanic mothers were overall more likely to initiate use after the start of pregnancy. While white mothers reported higher preconception initiation compared to Hispanic women, we did not find an association between the timing of pre-natal supplement use and preterm birth in this subgroup of the population. Among Hispanic women, the later pre-natal supplements were initiated, the higher the odds for preterm birth. The magnitude of this relationship is influenced by nativity, which may be a potential modifier of the relationship between pre-natal supplement use and preterm birth.

To our knowledge, this is the first study to investigate pre-natal supplement use including information on both preconception and the entire prenatal period among Hispanic women. Our

categorization of use is clinically important because not only do a majority of women continue to use pre-natal supplements once they initiate (**3.5.1 Table 1**) but, according to our results, use prior to conception and during early pregnancy influences the birth outcome.

In our study, no association between timing of pre-natal vitamin use and birth outcome was observed in non-Hispanic white mothers. This may be due to the limited added benefit of pre-natal vitamins for this group of women with potentially homogenous baseline nutritional status. On the other hand, most Hispanic women initiated pre-natal supplements once pregnancy commenced and likely had variable baseline micronutrient status upon entering pregnancy. As the strength of the association between timing of pre-natal vitamin initiation and preterm birth depends on nativity, it suggests baseline micronutrient status may be due to variations in dietary practices among Hispanic women by place of birth.

Previous studies show that dietary practices are sensitive to cultural changes that occur with migration. First-generation Mexican-American women of reproductive age on average consume significantly more vitamins and minerals (including vitamin A and C, folic acid, and calcium) relative to the recommended dietary allowance standards than second-generation Mexican-Americans (Harley et al, 2005; Guendelman & Abrams, 1995). Based upon intake below the estimated average requirement, the prevalence of inadequate intake of folate for pregnant US-born Mexican women is 1.4 times that of those born in Mexico (79.6% and 58.6%, respectively) (Harley et al, 2005). Additionally, Mexican-born women of reproductive age exhibit significantly higher intakes of fruits and vegetables compared to their US-born counterparts (Batis et al, 2011; Duffey et al, 2008). According to duration of residency in the US, the later Mexican women arrive to the US (childhood compared to adulthood) the better the quality of diet in pregnancy (Harley & Eskenazi, 2006). As Mexican-origin women move from

their country of origin to the US, the quality of diet declines with respect to micronutrients important for a healthy pregnancy. Thus, the attenuated relationship of pre-natal supplementation and preterm delivery among foreign-born Hispanic women compared to US-born women may be a result of the protective dietary practices maintained by foreign-born women that are lost in subsequent generations after migration.

Our findings are consistent with the Camden study of young, low-income, urban women (Scholl et al, 1997) that assessed initiation of pre-natal vitamins during the first two trimester of pregnancy on birth outcomes. This prospective cohort study of women in New Jersey from 1985 to 1995 reported an odds ratio of 0.66 (95% CI 0.47, 0.93) for women who initiated pre-natal vitamin use during the first and second trimester of pregnancy, compared with nonusers. Yet, this study failed to assess preconception use as part of the exposure definition (it was only assessed as a potential confounder) and was limited to very low-income, majority black women who accessed prenatal care by the second trimester. Thus, starting pre-natal vitamin supplementation in the first or second trimester may have benefited this group of women who likely have much lower micronutrient intakes than the general population.

Additionally, our findings are consistent with a previous study (Catov et al, 2011) that assessed the association between periconception multivitamin use and adverse birth outcomes. Data on periconception vitamin use, the 12 week interval 4 weeks prior to and 8 weeks after date of last menstrual period, was obtained from the Danish National Birth Cohort. Both timing and frequency of use were analyzed and compared to nonusers; it was found that regular pre- and post-conception multivitamin use in women with a prepregnancy BMI <25 kg/m^2 was associated with reduced risk of preterm birth. While this study incorporated the frequency in addition to

timing, it was limited to the periconception period and consisted mainly of women with European ancestry.

Our findings are limited due to the fact that supplement use may correlate with other lifestyle factors. Although we attempted to adjust for these factors, we cannot rule out the possibility of unmeasured confounding or incomplete adjustment of confounders due to the observational nature of our data. Additionally, information on supplement use was collected retrospectively for each time period and reporting error is possible.

Our results suggest that as many as 66% of white and 28% of Hispanic women use supplements before pregnancy. Moreover, it is estimated that 50% of pregnancies in the US are unplanned (Finer & Henshaw, 2006), with unintended births occurring disproportionately among minority, unmarried, and less educated women (Mosher et al, 2012; Finer & Henshaw, 2006). This investigation is important in providing information to better target potential intervention and educational efforts as our findings suggest that initiating pre-natal supplements once pregnancy is identified confers an increased risk of preterm birth, especially for US-born Hispanic women. Given that supplement use is a modifiable behavior, possible intervention strategies, such as prophylactic vitamin supplementation during child-bearing age, should be tailored to this population of women.

3.5 Tables and Figures

3.5.1 Table 1. Reported pre-natal vitamin use of UCLA Environment and Pregnancy Outcomes Study (EPOS) respondents (n=2,123).

Preconception use[a]	Prenatal use			n	Initiation of use
	Trimester 1[b]	Trimester 2[b]	Trimester 3[b]		
1	1	1	1	622	Preconception
1	1	1	0	17	
1	1	0	1	1	
1	1	0	0	27	
1	0	1	1	35	
1	0	1	0	8	
1	0	0	1	9	
1	0	0	0	8	
1	.	.	.	14	
0	1	1	1	999	Trimester 1
0	1	1	0	48	
0	1	0	1	2	
0	1	0	0	41	
0	0	1	1	124	Late prenatal/ never
0	0	1	0	26	
0	0	0	1	34	
0	0	0	0	58	
.	.	.	.	50	*Missing*

[a] "1" indicates respondent used vitamins during preconception period. Answered either "Yes- every day or almost every day" or "Yes- sometimes" to the question "Just before you got pregnant, were you taking multivitamins, pre-natal vitamins, or folic acid?"; "0" indicates respondent did not use vitamins during preconception period (answered "No").

[b] "1" indicates respondent used vitamins during indicated trimester. Respondent checked "yes" and the corresponding trimester in response to the question "Did you take any of the following vitamin supplements while you were pregnant?"; "0" indicates respondent did not use vitamins during indicated trimester (checked "No" and the corresponding trimester).

3.5.2 Table 2. Descriptive characteristics of UCLA Environmental Pregnancy Outcomes Study (EPOS) respondents by timing of pre-natal vitamin use (n=2,073).

		Initiation of use		
	All	Preconception	Trimester 1	Late prenatal/never
		n=741	n=1,090	n=242
Maternal ethnicity/nativity	n (%[a])	n (%[a])	n (%[a])	n (%[a])
Non-Hispanic White	426 (21)	281 (38)	126 (12)	19 (8)
Hispanic	1,647 (79)	460 (62)	964 (88)	223 (92)
US born	477 (29)	144 (31)	277 (29)	56 (25)
Foreign born	1,170 (71)	316 (69)	687 (71)	167 (75)
Maternal age (years)				
<20	225 (11)	44 (6)	136 (12)	45 (19)
20 to 24	457 (22)	111 (15)	284 (26)	62 (26)
25 to 29	545 (26)	169 (23)	319 (29)	57 (24)
30 to 34	517 (25)	229 (31)	240 (22)	48 (20)
35+	329 (16)	188 (25)	111 (10)	30 (12)
Maternal education (years)				
<8	330 (16)	71 (10)	204 (19)	55 (23)
9 to 11	489 (24)	109 (15)	300 (28)	80 (33)
12	563 (27)	188 (25)	311 (29)	64 (26)
13 to 15	292 (14)	108 (15)	157 (14)	27 (11)
16+	375 (18)	255 (34)	107 (10)	13 (5)
Initiation of prenatal care				
1st trimester	1,900 (92)	690 (93)	1,025 (94)	185 (76)
2nd, 3rd trimester, or never	158 (8)	44 (6)	60 (6)	54 (22)
Pre-pregnancy BMI (kg/m^2)				
<18.5	94 (5)	42 (6)	38 (3)	14 (6)
18.5 to 24.9	1,025 (53)	390 (53)	525 (48)	110 (45)
25.0 to 29.9	492 (26)	161 (22)	269 (25)	62 (26)
≥ 30.0	313 (16)	102 (14)	179 (16)	32 (13)
Alcohol use during pregnancy				
Yes	239 (12)	90 (12)	117 (11)	32 (13)
No	1,834 (88)	651 (88)	973 (89)	210 (87)
Home environmental tobacco smoke				
Yes	347 (17)	91 (12)	206 (19)	50 (21)
No	1,706 (83)	640 (86)	878 (81)	188 (78)
Previous PTB outcome				
Yes	18 (1)	10 (1)	8 (1)	0 (0)
No	2,055 (99)	731 (99)	1,082 (99)	242 (100)
Marital status				
Married or cohabitating	1,686 (82)	647 (87)	857 (79)	182 (75)
Single, divorced or separated	377 (18)	91 (12)	228 (21)	58 (24)

Primary source of payment for prenatal care				
Private insurance	788 (38)	411 (55)	326 (30)	51 (21)
Other insurance or no insurance	1,280 (62)	326 (44)	763 (70)	191 (79)
Birth Outcomes				
LBW[b]	176 (8)	57 (8)	92 (8)	27 (11)
PTB[c]	829 (40)	278 (38)	444 (41)	107 (44)
TNW[d]	1,068 (52)	406 (55)	554 (51)	108 (45)

[a] Percentages may not add up to or exceed 100% due to missing information and rounding.

[b] Low birthweight (LBW) birth defined as >37 weeks gestation and <2,500 grams.

[c] Preterm birth (PTB) defined as ≤37 weeks gestation.

[d] Term, normal weight (TNW) birth defined as >37 weeks gestation and ≥2,500 grams.

3.5.3 Table 3. Descriptive characteristics of UCLA Environment and Pregnancy Outcomes Study (EPOS) Hispanic respondents by nativity (n=1,647).

	US born n=477	Foreign born n=1,170
Maternal heritage	%[a]	%[a]
Mexican/Mexican-American/Chicano	86	79
Puerto Rican	2	0
Cuban	1	0
Central/South American	8	20
Other Spanish/Hispanic	4	0
Maternal characteristics and behaviors		
Maternal age (years)	n (%[a])	n (%[a])
<20	102 (21)	117 (10)
20 to 24	158 (33)	270 (23)
25 to 29	135 (28)	321 (27)
30 to 34	64 (13)	294 (25)
35+	18 (4)	168 (14)
Maternal education (years)		
<8	13 (3)	315 (27)
9 to 11	125 (26)	351 (30)
12	189 (40)	322 (28)
13 to 15	105 (22)	105 (9)
16+	41 (9)	61 (5)
Initiation of prenatal care		
1st trimester	429 (90)	1,065 (92)
2nd, 3rd trimester, or never	46 (10)	92 (8)
Pre-pregnancy BMI (kg/m^2)[b]		
<18.5	15 (3)	51 (5)
18.5 to 24.9	224 (49)	532 (50)
25.0 to 29.9	112 (25)	313 (29)
≥ 30.0	104 (23)	168 (16)
Alcohol use during pregnancy		
Yes	58 (12)	91 (8)
No	419 (88)	1,079 (92)
Home environmental tobacco smoke		
Yes	111 (23)	172 (15)
No	362 (77)	985 (85)
Marital status		
Married or cohabitating	328 (69)	969 (83)
Single, divorced or separated	148 (31)	193 (17)
Primary source of payment for prenatal care		
Private insurance	206 (43)	206 (18)
Other insurance or no insurance	271 (57)	961 (82)
Birth outcomes		

LBW[b]	46 (10)	100 (9)
PTB[c]	204 (43)	478 (41)
TNW[d]	227 (48)	592 (51)

[a] Percentages may not add up to or exceed 100% due to missing information and rounding.
[b] Low birthweight (LBW) birth defined as >37 weeks gestation and <2,500 grams.
[c] Preterm birth (PTB) defined as ≤37 weeks gestation.
[d] Term, normal weight (TNW) birth defined as >37 weeks gestation and ≥2,500 grams.

3.5.4 Table 4. Associations among prenatal vitamin use timing and birth outcome in Non-Hispanic White and Hispanic Environment and Pregnancy Outcomes Study (EPOS) respondents.

	Prenatal vitamin use	PTB[a]/TNW[b]	Unadjusted OR	PTB[a]/TNW[b]	Adjusted OR[c]	95% CI
All respondents	Preconception	829/1,068	1.00	752/978	1.00	-
	First trimester		1.17		1.19	(0.95, 1.50)
	Late prenatal/never		1.45		1.44	(1.02, 2.03)
Non-Hispanic White	Preconception	147/249	1.00	137/237	1.00	-
	First trimester		0.76		0.84	(0.50, 1.43)
	Late prenatal/never		0.85		0.85	(0.25, 2.85)
All Hispanic	Preconception	682/819	1.00	615/741	1.00	-
	First trimester		1.20		1.34	(1.04, 1.73)
	Late prenatal/never		1.46		1.63	(1.13, 2.36)
Hispanic US-born	Preconception	204/227	1.00	193/215	1.00	-
	First trimester		1.52		1.74	(1.07, 2.83)
	Late prenatal/never		2.25		2.14	(1.03, 4.43)
Hispanic foreign-born	Preconception	478/592	1.00	422/526	1.00	-
	First trimester		1.09		1.23	(0.90, 1.67)
	Late prenatal/never		1.25		1.52	(0.98, 2.35)

[a] Preterm birth (PTB) defined as ≤37 weeks gestation.

[b] Term, normal weight (TNW) birth defined as >37 weeks gestation and ≥2,500 grams.

[c] Adjusted for maternal race/ethnicity, maternal age, maternal education, trimester of prenatal care initiation, pre-pregnancy BMI, and primary source of payment for prenatal care.

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Chapter 4: Prenatal folic acid supplement initiation and risk of adverse early childhood respiratory health: A Los Angeles population-based study

4.1 Introduction

Due to physiological changes that take place during pregnancy, women experience an increased requirement of both energy and nutrients. For example, gravidas have an approximately 18-76% increased need for folate compared to non-pregnant women (Ladipo, 2000). While these requirements can generally be met by an adequate diet, suboptimal micronutrient intake is more common during pregnancy (Blumfield et al, 2013) and likely exacerbated by suboptimal dietary intake prior to conception especially among such groups as Hispanic and low-income women (Gahche et al, 2011). Thus, primarily to prevent neural tube defects, it is recommended that women planning a pregnancy consider taking daily supplements containing 400-800ug of folic acid preconception and through the first trimester (USPSTF, 2009), as folic acid in supplements and fortified foods has 1.7 times the bioavailability of folate naturally present in the diet (IOM, 1998).

In the United States, asthma, characterized by airway inflammation and bronchial hyperactivity (Eder et al, 2006), is a leading cause of chronic childhood illness (Adams et al, 1999) and disability (Newacheck & Halfon, 2000). In early life, not all types of wheeze eventually become asthma and several phenotypes have been described in the literature including patterns of 'early transient,' 'persistent' and 'late-onset' wheeze (Martinez et al, 1995). As clinical asthma usually develops between the ages of 5 and 6, wheeze before this age is likely a combination of 'transient' and 'persistent wheeze' (Maslova & Hansen, 2014) and early

wheezing may reflect a predisposition for asthma (Martinez et al, 1995). Apart from genetics, multiple factors are thought to contribute to the risk of asthma including prenatal exposures and dietary factors (von Mutius & Hartert 2013).

The impact of folic acid and pre-natal supplement use during pregnancy on the risk of early adverse respiratory health has been a topic of increasing interest. In 2008, a study of transgenic mice reported that a diet high in methyl donors, mimicking prenatal supplementation with folic acid, produced offspring with increased global methylation and an allergic asthma phenotype compared to dams on a standard chow diet (Hollingsworth et al). However, it has yet to be determined whether maternal supplementation during pregnancy changes fetal DNA methylation (Crider et al, 2012) and ultimately risk of childhood asthma.

Research in US populations is of particular interest in the light of the mandatory folic acid fortification program implemented in 1998 (FDA, 1996). A recent study of Tennessee Medicaid enrolled pregnant women found that filling folic acid prescriptions in the first trimester (nearly all of which were pre-natal supplements) increased risk of having children with asthma at 5 years of age compared to those not filling prescriptions during pregnancy (Veeranki et al, 2015). On the other hand, a study of Massachusetts women assessed folic acid exposure in pregnancy from both diet and pre-natal supplement use and found no association between combined intakes and risk of childhood wheeze or respiratory infections at 2 years of age (Litonjua et al, 2006). Additionally, in a cohort study of Boston mothers, self-reported maternal folic acid intake in pregnancy (from supplements, including pre-natal vitamins) was not associated with doctor diagnosed asthma in children six years of age (Martinussen et al, 2012). The inconsistency of findings may be due to the heterogeneity in the assessment of exposure: the method of folic acid assessment (whether through diet, supplement or both), timing of intake

(gestational week, month, trimester), method used to categorize supplement intake for analysis (binary, categorical based on dose, continuous); or variations in outcome measures (asthma, wheeze, and other respiratory conditions), offspring age; or variations in baseline micronutrient status of mothers (Brown et al, 2013).

Because of proven benefits of folate supplementation during pregnancy in preventing neural tube defects (USPSTF, 2009), it is important to better understand whether prenatal folic acid supplementation is associated with adverse respiratory outcomes in offspring. Both lung and immune system development begin 3 weeks after fertilization and continue throughout gestation and postnatal life (Joshi & Kotecha, 2007; Holt & Jones, 2000). In this study, we investigate whether early supplementation increases the risk of adverse child respiratory health outcomes in a population-based study of majority immigrant Hispanic women residing in Los Angeles. We explore the timing of folic acid supplement initiation during pregnancy and its association with wheeze and lower respiratory tract infections in offspring at approximately three years of age.

4.2 Methods

Study Design and Population

The UCLA Environment and Child Health Outcomes Study (ECHOS) is a follow-up study of women who were first enrolled in the UCLA Environment and Pregnancy Outcomes Study (EPOS). The original goals of these studies were to examine the effects of ambient air pollution on adverse birth outcomes (EPOS) and adverse respiratory outcomes in children (ECHOS). EPOS is a case-control study nested within the 2003 birth cohort of all women who

resided in one of 111 ZIP codes in Los Angeles County. The details of subject selection for EPOS are described elsewhere (Ritz et al. 2007). Briefly, Los Angeles County electronic birth certificate records were used to select live singleton births to mothers residing near air pollution monitoring stations and/or major roadways. All cases of preterm birth (<37 weeks gestation) and low birth weight (<2500 grams) were included from 24 zip codes near air monitoring stations, and a random sample of 30% of cases from another 87 zip code areas. While 6,374 women were invited to participate, a total of 2,543 women were enrolled in EPOS 3-6 months postpartum (a response rate of 40%). Mothers were interviewed in English or Spanish by telephone, by mail survey, and during home visits.

In 2006-2007, a follow-up survey was conducted to collect information on respiratory health of offspring at on average 3.5 years of age. Of the original EPOS participants, approximately 50% (n=1,201) participated in ECHOS and mothers were interviewed in English or Spanish by telephone or mail survey.

Vitamin use

The EPOS survey instrument elicited information on timing and frequency of various vitamins used during preconception and the prenatal period. Prenatal vitamin use was assessed by asking: "Did you take any of the following vitamin supplements while you were pregnant: pre-natal vitamins, multivitamins, vitamin C, iron and 'other' supplements." For the open response supplement category 'other,' respondents filled-in vitamins consumed during pregnancy that were not included on the provided list (including folic acid). For all supplements, respondents were asked to indicate use (yes/no) of the individual supplements during each trimester. Additionally, respondents were asked to report the frequency of vitamin use during

the trimesters in which they indicated use, with the following response categories: "once a month," "once a week," about 3 days a week," and "every day." Data on dose or brand of supplements was not collected.

Based upon responses for both folic acid (from 'other' vitamin category) and pre-natal supplements, overall folic acid use was categorized according to whichever supplement was initiated first (**4.5.1 Table 1**). We list the possible combinations of use by trimester in **4.5.2 Table 2** and overall folic acid use was categorized using the following mutually exclusive groups: (1) first trimester initiation; (2) late prenatal (trimester 2 or 3) initiation; (3) Never. To assess associations of first trimester use on child health outcomes, initiation was dichotomized into first trimester and late/no initiation (from this point termed late initiation).

Respiratory outcomes

In the 2006-2007 follow-up interviews, we assessed child respiratory health via maternal report. In addition to the International Study of Asthma and Allergies in Childhood (ISAAC) core questions on asthma and wheeze (Asher et al, 1995), the survey also solicited information on lower respiratory tract infections (LRTI). To assess wheeze in the child, respondents were asked: "has your child ever had wheezing or whistling in the chest at any time in the past" (ever wheeze) followed by "has your child had wheezing or whistling in the chest in the past 12 months" (current wheeze). Additionally, mothers who identified their child as having suffered from pneumonia, bronchiolitis, bronchitis, croup or respiratory simplex virus were identified as having experienced LRTI.

Covariate assessment

Information on demographics and health behaviors during pregnancy was obtained from California electronic birth records and the EPOS survey 3-6 months postpartum, respectively. Covariates include mother's race/ethnicity (non-Hispanic white, Hispanic white, Black, Asian/Other) and nativity (US born, foreign born), mother's age at pregnancy (<20, 20-24, 25-29, 30+), mother's education at the time of pregnancy (≤11 years, 12 years, ≥13 years), use of preconception vitamins (yes, no), initiation of prenatal care (first trimester, after first trimester/never), alcohol use during pregnancy (yes, no), home environmental tobacco smoke (ETS; yes, no), pre-pregnancy BMI (<24.9 kg/m^2, ≥25.0 kg/m^2), marital status (married/cohabitating, single/divorced/separated), primary source of payment for prenatal care (private health insurance, other/none), parity (only child, ≥1 sibling), and birth outcome (preterm, term birth). Maternal history of atopy (including eczema, asthma, and hay fever), duration of exclusive breastfeeding (<3 months, ≥3months), child attendance to daycare or preschool (yes, no), infection during pregnancy (yes, no), and housing characteristics (mold or pests in the home in the past year) were obtained from the ECHOS survey.

Statistical methods

We used Poisson regression models with robust error variance and a log link function to estimate risk ratios (RRs) for timing of folic acid initiation (first trimester, late/never) and early adverse child health outcomes separately (ever wheeze, current wheeze, and LRTI). Analyses were limited to those with a response to folic acid supplement use in pregnancy (n=1,176). All previously mentioned covariates were assessed as potential confounders and those that changed the crude point estimate by approximately 5% or more were retained in the final models.

Approximately half the original EPOS respondents were unable to be re-contacted for the ECHOS follow-up study (53%). Compared to baseline (EPOS) respondents, censorship at follow-up was associated with mother's race/ethnicity, age, education and folic acid use. After adjusting for the other covariates, supplement initiation was no longer associated with censoring. In sensitivity analyses, inverse probability censoring weights (IPCW) accounting for these four factors were applied to assess the impact of loss to follow-up.

The original EPOS nested case-control study oversampled adverse birth outcomes and our follow-up study population consisted of 37.5% preterm births. In separate sensitivity analyses, the sample was reweighed to reflect a 10% prevalence of preterm birth as we would expect to observe in the general population.

Additionally, previous research suggests offspring of atopic mothers have a higher risk for asthma compared to children of women with no such history (Dold et al, 1992). Thus, we explored heterogeneity of the association between folic acid initiation and early child respiratory outcomes by maternal history of hay fever, eczema or asthma (atopy).

Data was analyzed using the SAS statistical software package version 9.3 (SAS Institute, Inc. Cary, North Carolina). This work was approved by the UCLA Office for the Protection of Human Subjects and the California Committee for the Protection of Human Subjects.

4.3 Results

Among study participants, the vast majority of women initiated folic acid use in the first trimester and once initiated, most reported continued use throughout pregnancy (**4.5.2 Table 2**). According to maternal reports of offspring outcomes, one fourth of children experienced wheeze

in their lifetime with 56% of these children having had at least one episode of wheeze in the 12 months prior to the survey (**4.5.3 Table 3**).

The majority of women identified as Hispanic with approximately 70% being foreign-born (**4.5.3 Table 3**) of Mexican, Mexican-American or Chicano descent (*data not shown*). Overall, respondents were mostly married women who initiated prenatal care in the first trimester, did not use alcohol or smoke and were not exposed to ETS in the home during pregnancy. Late pregnancy folic acid initiators were more likely to be low income (as measured by primary payer of prenatal care) Hispanic, younger, less educated, and more likely to begin prenatal care late in pregnancy compared to those who reported first trimester use. After adjustment for potential confounders, the timing of folic acid supplement initiation was not associated with adverse early child respiratory outcomes and results did not change after reweighing for preterm birth or applying censoring weights (**4.5.4 Table 4**).

Compared to mothers without a history of atopy, mothers with such history were older, more educated, US born non-Hispanic white women with higher incomes (as measured by primary payer of prenatal care) (**4.5.5 Table 5**). In stratified analyses, we observed possible effect measure modification as the strength of the association varied strongly by maternal history of atopy (**4.5.6 Figure 1**). Among atopic mothers, late pregnancy initiation of supplements was associated with an increased risk of wheeze in the first three years of life and wheeze in the past year, while no association was observed for lower respiratory tract infection. Additionally, no association was observed among non-atopic mothers.

4.4 Discussion

Utilizing data from a follow-up study of participants to a population based case-control study nested within the 2003 birth cohort of Los Angeles, we found that early pregnancy initiation of folic acid does not increase the risk of adverse child respiratory outcomes by 3.5 years of age. Overall, we did not find an association between timing of supplement initiation during pregnancy and child respiratory outcomes and these findings were robust to IPCW and population re-weighting to reflect 10% prevalence of preterm birth. Yet, we did observe an increased risk for wheeze in the first three years of life and wheeze in the past year among offspring of atopic mothers who did not initiate folic acid supplementation in the first trimester of pregnancy. The mostly immigrant, Hispanic study population reported wheeze in the first three years of life in a quarter of their children, wheeze in the 12 months prior to interview and lower respiratory tract infection for 14% and 22% of children, respectively.

The lack of association between timing of folic acid use and respiratory outcomes among study respondents overall is consistent with a previous study of US women in the Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM) study (Martinussen et al, 2012). However, PRAM enrolled a majority of white, educated, high socioeconomic status women of whom half had been diagnosed with asthma. While this study benefitted from prospective assessment of vitamin use (derived from maternal reports of supplements including pre-natal vitamins), only information from the month before conception through the third month of pregnancy was collected. Moreover, outcomes in offspring were assessed at age 6 and a positive outcome for current asthma required both a health professional diagnosis of asthma and reports of wheeze in the last year only. No association was observed between folic acid use and asthma at 6 years of age, neither during the preconception period nor first trimester. Our study expands on these

findings by assessing folic acid supplement use throughout pregnancy in a predominantly Hispanic and immigrant population.

Previous research has identified associations between dietary intake and asthma among adults suggesting those with asthma have lower dietary intakes of micronutrients compared with healthy controls (Patel et al, 2006; Berthon et al, 2013). Thus as nutrient requirements increase during pregnancy, suboptimal micronutrient intake may result among atopic pregnant women. The intrauterine environment plays an integral role in the development of future health outcomes (Goldenberg & Culhane, 2007; von Mutius & Hartert 2013) through permanent adaptations to the prenatal environment (Barker & Osmond, 1986; Halfon et al, 2014). As a nation, US pregnant women's median daily dietary intake of folate is approximately 40% below the recommended daily intake (Blumfield et al, 2013) and poor maternal nutrition during early pregnancy may have a negative impact on the growth and development of the fetus, which in turn may affect risk of early childhood respiratory health. While atopic women were older, more educated, US born non-Hispanic white women with higher incomes, in the present study we found that children born to atopic mothers who initiate folic acid supplement use late in pregnancy had 1.7 times the risk of wheeze in the first three years of life and 1.9 times the risk of current wheeze compared to first trimester initiating mothers. No association was found among non-atopic women.

To our knowledge, this is the first study to investigate folic acid initiation and respiratory outcomes in a predominantly Hispanic population of US women. We were limited in our measure of folic acid intake among respondents as our definition of use included both folic acid and pre-natal supplements. Detailed information on the brand or composition of supplements was not collected and while the categorization of folic acid initiation was mainly driven by

timing of pre-natal supplement use, a recent study found that 99% of folic-acid containing prescriptions filled by women during pregnancy were pre-natal vitamins (Veeranki et al, 2015). Moreover, supplement use was based on maternal report only and may have resulted in some measurement error in the timing of initiation Although we had detailed information on a large number of potential confounders and adjusted for these factors, we cannot rule out the possibility of unmeasured confounding. Finally, health outcomes in children were assessed at an average of 3.5 years of age thus we captured early respiratory conditions and likely some cases of transient wheeze (Maslova & Hansen, 2014).

In thus study, we found an increased risk of wheeze among three year old offspring of atopic mothers who initiate pre-natal supplements late in pregnancy compared to first trimester initiators. While our findings support the current recommendations of early folic acid supplementation (USPSTF, 2009), this novel contribution to the literature calls for further investigation into both maternal history of atopy as a potential modifier of the relationship between folic acid use and adverse early respiratory health and the biologic mechanisms that may underlie this relationship. Ideally, this additional information could then be used to tailor public health interventions to this high risk group of pregnant women to improve offspring respiratory health.

4.5 Tables and Figures

4.5.1 Table 1. Distribution of folic acid initiation by initiation of pre-natal supplements among UCLA Environment and Pregnancy Outcomes Survey (EPOS) respondents (n=2,543).

Pre-natal supplement initiation	Folic acid initiation				Any folic acid supplement
	Trimester 1 (n=191)	Trimester 2/3 (n=34)	Never (n=5)	Missing (n=2,313)	
Trimester 1 (n=2,099)	173	9	3	1,914	2,117
Trimester 2/3 (n=285)	8	20	0	257	364
Never (n=97)	10	5	2	80	
Missing (n=62)	0	0	0	62	62

4.5.2 Table 2. Distribution of folic acid supplement initiation according to censorship of UCLA Environment and Child Health Outcomes Survey (ECHOS) respondents.

Vitamin use group	Trimester 1	Trimester 2	Trimester 3	Folic acid categorization	EPOS (All subjects)		ECHOS (Not lost to follow-up)	
1	1	1	1	Tri 1	1,942	2,117 (85)	944	1,025 (87)
2	1	1	0		85		38	
3	1	0	1		7		4	
4	1	0	0		83		39	
5	0	1	1	Tri 2/3/never	190	364 (15)	85	151 (13)
6	0	1	0		43		14	
7	0	0	1		49		18	
8	0	0	0		82		34	
				Total	*2,481*		*1,176*	

4.5.3 Table 3. Descriptive characteristics of UCLA Environment and Child Health Outcome Survey (ECHOS) respondents by folic acid initiation.

	All	Trimester 1	Late/never
	n=1,176	n=1,025 (87)	n=151 (13)
Maternal ethnicity/nativity	n (%[a])	n (%[a])	n (%[a])
Non-Hispanic White	295 (25)	282 (28)	13 (9)
Hispanic	703 (60)	588 (58)	115 (76)
US born	223 (32)	195 (33)	28 (24)
Foreign born	480 (68)	393 (67)	87 (76)
Black	70 (6)	62 (6)	8 (5)
Asian/Other	99 (8)	84 (8)	15 (10)
Maternal age (years)			
<24	280 (24)	227 (22)	53 (35)
25 to 29	294 (25)	263 (26)	31 (21)
30 to 34	345 (29)	306 (30)	39 (26)
≥ 35	257 (22)	229 (22)	28 (19)
Maternal education (years)			
≤ 11 years	313 (27)	248 (25)	65 (44)
12 years	269 (23)	229 (23)	40 (27)
≥ 13 years	570 (49)	528 (53)	42 (29)
Preconception vitamins			
Yes	518 (44)	474 (46)	44 (29)
No	658 (56)	551 (54)	107 (71)
Initiation of prenatal care			
1st trimester	1,096 (94)	977 (96)	119 (80)
2nd, 3rd trimester, or never	73 (6)	44 (4)	29 (20)
Alcohol use during pregnancy			
Yes	159 (14)	136 (13)	23 (15)
No	1,017 (86)	889 (87)	128 (85)
Home environmental tobacco smoke			
Yes	177 (15)	152 (15)	25 (17)
No	992 (85)	868 (85)	124 (83)
Pre-pregnancy BMI (kg/m^2)			
<24.9 kg/m^2	687 (61)	600 (61)	87 (60)
GE 25.0 kg/m^2	437 (39)	378 (49)	59 (40)
Marital status			
Married or cohabitating	974 (83)	865 (85)	109 (73)
Single, divorced or separated	199 (17)	158 (15)	41 (27)
Primary source of payment for prenatal care			
Private insurance	607 (52)	560 (55)	47 (31)
Other insurance or no insurance	567 (48)	463 (45)	104 (69)
Maternal history of hay fever, eczema, or asthma			
Yes	266 (23)	249 (24)	17 (11)
No	910 (77)	776 (76)	134 (89)
Infection during pregnancy			
Yes	307 (26)	270 (26)	37 (25)
No	867 (74)	753 (74)	114 (76)

Child's sex			
Male	592 (50)	517 (50)	75 (50)
Female	584 (50)	508 (50)	76 (50)
Birth outcome			
Preterm birth	441 (38)	382 (37)	59 (39)
Term birth	735 (62)	643 (63)	92 (61)
Exclusively breastfed child			
< 3 months	559 (48)	481 (47)	78 (52)
GE 3 months	617 (52)	544 (53)	73 (48)
Siblings			
None	477 (41)	434 (42)	43 (28)
≥ 1	699 (59)	591 (58)	108 (72)
Child attended day care or preschool			
Yes	637 (54)	570 (56)	67 (44)
No	533 (46)	449 (44)	84 (56)
Housing characteristics[a]			
Mold	224 (19)	188 (19)	36 (24)
Any reported pests in the home	775 (66)	677 (66)	98 (65)
Rats	43 (4)	37 (4)	6 (4)
Mice	119 (10)	107 (10)	12 (8)
Cockroaches	268 (23)	217 (21)	51 (34)
Child respiratory health outcomes[b]			
Ever wheeze	299 (26)	261 (26)	38 (26)
Current wheeze[c]	166 (14)	146 (14)	13 (20)
Lower respiratory tract infection[d]	253 (22)	227 (22)	26 (17)

[a] Housing characteristics including mold and pests were asked in the ECHOS survey. Mothers were asked to report presence of either in the past 12 months.

[b] Offspring health outcomes measured at 3 years of age.

[c] Defined as reported wheeze in the past 12 months.

[d] Includes reports of any of the following infections: pneumonia, bronchiolitis, bronchitis, croup or respiratory simplex virus.

4.5.4 Table 4. Associations between folic acid initiation and early child respiratory outcomes in UCLA Environment and Child Health Outcomes Survey (ECHOS) respondents.

	Crude RR (95% CI)		Adjusted RR (95% CI)[a]			Adjusted RR + PTB Weight (95% CI)[b]			Adjusted RR + IPCW (95% CI)[c]		
	First trimester	Late pregnancy	cases/non-cases	First trimester	Late pregnancy	cases/non-cases	First trimester	Late pregnancy	cases/non-cases	First trimester	Late pregnancy
Ever wheeze	1.00	1.00 (0.74, 1.34)	292/847	1.00	1.19 (0.89, 1.59)	268/869	1.00	1.33 (0.95, 1.86)	604/1,814	1.00	1.19 (0.88, 1.61)
Current wheeze[d]	1.00	0.93 (0.60, 1.44)	163/980	1.00	1.16 (0.76, 1.78)	149/993	1.00	1.31 (0.80, 2.14)	332/2,094	1.00	1.16 (0.75, 1.81)
LRTI[e]	1.00	0.78 (0.54, 1.12)	252/895	1.00	0.97 (0.68, 1.38)	256/890	1.00	1.07 (0.71, 1.61)	502/1,934	1.00	1.01 (0.69, 1.49)

[a] Adjusted for: mother's race/ethnicity, nativity, education, and history of hay fever, eczema or asthma.

[b] Adjusted for all variables in adjusted model in addition to applying weights to reflect an expected 10% preterm birth outcome.

[c] Adjusted for all variables in adjusted model in addition to applying standardized inverse probability censoring weights.

[d] Defined as reported wheeze in the past 12 months.

[e] Lower respiratory tract infection (LRTI); includes reports of any of the following infections: pneumonia, bronchiolitis, bronchitis, croup or respiratory simplex virus.

4.5.5 Table 5. Descriptive characteristics of UCLA Environment and Child Health Outcome Survey (ECHOS) respondents by maternal history of atopy (n=1,176).

	Maternal history of atopy	No maternal history of atopy	
	n=266 (23)	n=910 (77)	p-value
Maternal ethnicity/nativity	n (%[a])	n (%[a])	
Non-Hispanic White	126 (48)	169 (19)	
Hispanic	82 (31)	621 (69)	
Black	24 (9)	46 (5)	
Asian/Other	32 (12)	67 (7)	*<0.0001*
Maternal nativity			
US born	192 (72)	367 (40)	
Foreign born	73 (28)	542 (60)	*<0.0001*
Maternal age (years)			
<24	48 (18)	232 (25)	
25 to 29	49 (18)	245 (27)	
30 to 34	77 (29)	268 (29)	
≥ 35	92 (35)	165 (18)	*<0.0001*
Maternal education (years)			
≤ 11 years	27 (10)	286 (32)	
12 years	38 (15)	231 (26)	
≥ 13 years	196 (75)	374 (42)	*<0.0001*
Preconception vitamins			
Yes	159 (60)	359 (39)	
No	107 (40)	551 (61)	*<0.0001*
Folic acid supplement initiation			
First trimester	249 (94)	776 (85)	
Trimester 2/3/never	17 (6)	134 (15)	*0.0004*
Initiation of prenatal care			
1st trimester	256 (96)	840 (93)	
2nd, 3rd trimester, or never	10 (4)	63 (7)	*0.0567*
Alcohol use during pregnancy			
Yes	46 (17)	113 (12)	
No	220 (83)	797 (88)	*0.0408*
Home environmental tobacco smoke			
Yes	32 (12)	145 (16)	
No	233 (88)	759 (84)	*0.1134*
Pre-pregnancy BMI (kg/m^2)			
<24.9 kg/m^2	163 (62)	524 (61)	
GE 25.0 kg/m^2	98 (38)	339 (39)	*0.3462*
Marital status			
Married or cohabitating	237 (89)	737 (81)	
Single, divorced or separated	29 (11)	170 (19)	*0.0027*
Primary source of payment for prenatal care			
Private insurance	205 (77)	402 (44)	
Other insurance or no insurance	61 (23)	506 (56)	*<0.0001*
Infection during pregnancy			

Yes	96 (36)	211 (23)	
No	170 (64)	697 (77)	*<0.0001*
Child's sex			
Male	131 (49)	461 (51)	
Female	135 (51)	449 (49)	*0.6855*
Birth outcome			
Preterm birth	103 (39)	338 (37)	
Term birth	163 (61)	572 (63)	*0.6398*
Exclusively breastfed child			
< 3 months	107 (40)	452 (50)	
GE 3 months	159 (60)	458 (50)	*0.0067*
Siblings			
None	115 (43)	362 (40)	
≥ 1	151 (57)	548 (60)	*0.313*
Child attended day care or preschool			
Yes	171 (65)	466 (51)	
No	93 (35)	440 (49)	*0.0001*
Housing characteristics[a]			
Mold	53 (20)	171 (19)	*0.68*
Any reported pests in the home	207 (78)	568 (62)	*<0.0001*
Rats	9 (3)	34 (4)	*0.7874*
Mice	28 (11)	91 (10)	*0.8023*
Cockroaches	50 (19)	218 (24)	*0.0776*
Child respiratory health outcomes[b]			
Ever wheeze	105 (40)	194 (21)	*<0.0001*
Current wheeze[c]	59 (22)	107 (12)	*<0.0001*
Lower respiratory tract infection[d]	93 (35)	160 (18)	*<0.0001*

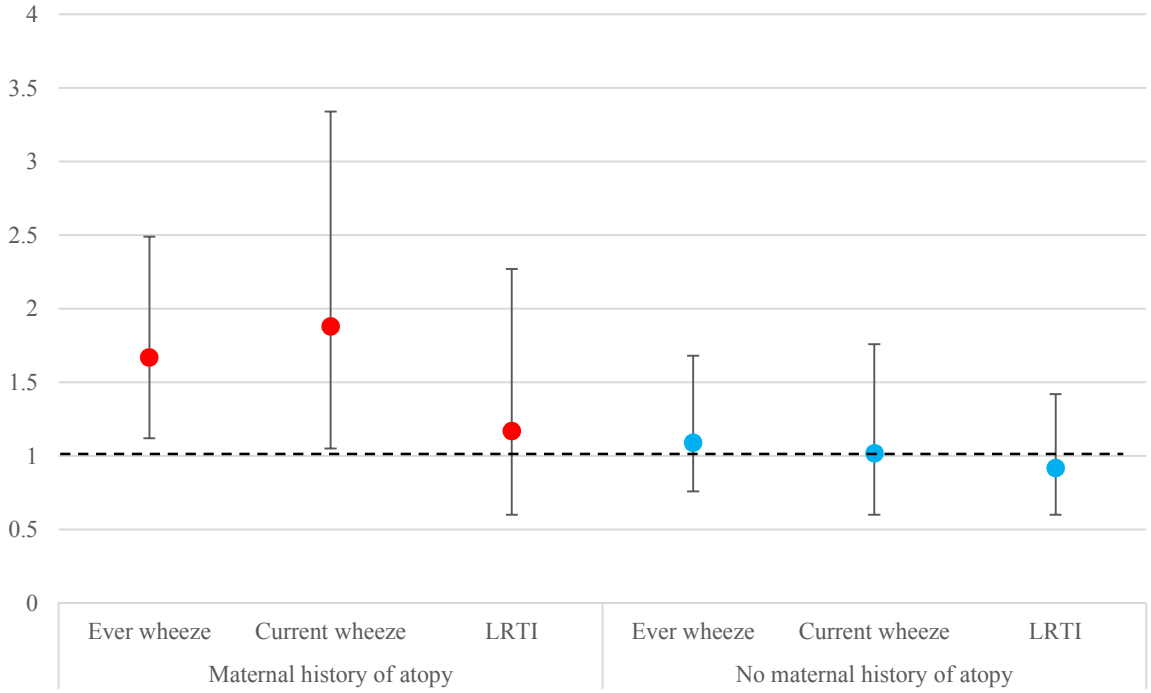
[a] Housing characteristics including mold and pests were asked in the ECHOS survey. Mothers were asked to report presence of either in the past 12 months.

[b] Offspring health outcomes measured at 3 years of age.

[c] Defined as reported wheeze in the past 12 months.

[d] Includes reports of any of the following infections: pneumonia, bronchiolitis, bronchitis, croup or respiratory simplex virus.

4.5.6 Figure 1. Adjusted risk ratios[a] for folic acid initiation and early child respiratory outcomes among UCLA Environment and Child Health Outcomes Survey (ECHOS) respondents (n=1,176).



[a] Adjusted for: mother's race/ethnicity, nativity, and education.

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Chapter 5: Public health significance

According to the lifecourse perspective and the 'Barker hypothesis', the prenatal environment plays an integral role in the development of both adverse birth and early childhood health outcomes. Specifically, maternal nutrition in pregnancy may serve as a programming stimulus to alter fetal development and susceptibility to future disease. In the US preterm birth remains a prominent public health concern as infants born premature are at higher risk of death and disability. Additionally, premature birth is associated with both recurrent preterm birth and asthma, the leading cause of chronic childhood illness and disability.

This dissertation examined the relationship between maternal nutrition in pregnancy through supplement initiation and WIC enrollment and offspring outcomes, including birth and early child respiratory health. In the first study of WIC enrollment and recurrent preterm birth, we identified high risk subgroups of eligible non-enrollees. Our findings highlight the importance of future investigation into reasons why eligible women do not enroll in the program in order to better inform targeted interventions to increase WIC participation among these higher risk pregnancies. The last two studies focused on the relationship between supplement initiation in pregnancy and both birth outcomes and early offspring respiratory health. Despite being encouraged to take folic acid containing supplements, suboptimal micronutrient intake is common in pregnancy, especially among Hispanic women. Findings from our population-based case-control study suggest that nativity may modify the relationship between pre-natal supplement use and preterm birth possibly due to underlying differences in diet composition of Hispanic women by place of birth. Additionally, findings from the follow-up study of case-control respondents highlight the importance of early folic acid supplement initiation among

atopic mothers as these women are at high risk of having offspring with adverse respiratory conditions. As this finding is a novel contribution to the literature, it calls for further investigation into both maternal history of atopy as a potential modifier of the relationship between folic acid use and adverse early respiratory health and the biologic mechanisms that may underlie this relationship. Findings from both studies are in accordance with current early pregnancy folic acid containing supplement recommendations and the identification of high risk subgroups of pregnant women allows for tailored public health messages aimed at changing this modifiable behavior in high risk women.